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Pharmacology of Antimalarial Drugs, Current Anti-malarials

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Currently available antimalarial drugs can be classified into four broad categories according to their chemical structures and modes of action.

1. Arylamino alcohol compounds: quinine, quinidine, chloroquine, amodiaquine, mefloquine, halofantrine, piperaquine, and lumefantrine
2. 8-Aminoquinoline: primaquine and tafenoquine
3. Antifolate compounds: sulfadoxine, pyrimethamine, proguanil, chlorproguanil, and trimethoprim
4. Artemisinin compounds: artemisinin, artesunate, artemether, β-arteether, and dihydroartemisinin
5. Others: atovaquoneand antibacterial drugs (tetracycline, doxycycline, and clindamycin)

Arylamino Alcohol Antimalarials

Chloroquine

Chloroquine was first synthesized by Bayer in Germany as early as 1934. The initial clinical studies were performed by German scientists just before World War II. However, the drug was reported to be too toxic for human use and not introduced for general use at that time. By late 1944, in the intensive search for an effective antimalarial drug during World War II, US workers synthesized 25 different 4-aminoquinoline derivatives, with the objective of discovering more effective and less toxic suppressive agents than quinacrine. Of these compounds, chloroquine proved the most promising and later underwent extensive clinical studies. Since then, chloroquine had been used as the drug of choice for treatment of human malaria all over the world until the advent of chloroquine resistance in *Plasmodium falciparum* in the early 1960s. Clinical treatment failures of *P. falciparum* were first noted in Thailand almost at the same time as in South America. Chloroquine-resistant *P. falciparum* has since then spread relentlessly to virtually all areas of the world except Central America, North Africa, and parts of Western Asia.

Chemistry and Physical Properties

Chloroquine [7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline: Fig. 1a] is a weakly basic tertiary amine synthetic antimalarial agent which is a 4-aminoquinoline derivative. It has a quinoline ring with a side chain identical with that of quinacrine. The chlorine atom in the seventh position appears to be crucial to the antimalarial activity of all 4-aminoquinoline antimalarials. The drug is used

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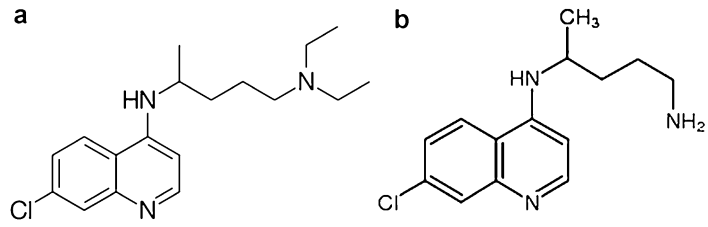


Pharmacology of Antimalarial Drugs, Current Anti-malarials, Fig. 1 Chemical structures of (**a**) chloroquine and (**b**) mono-desethyl chloroquine

as a racemic mixture of equal amounts of S(+) and R (−) chloroquine.

Chloroquine is a white or slightly yellow, odorless, crystalline powder with a bitter taste. It is poorly soluble in water, but soluble in diluted acid, chloroform, and ether. Chloroquine phosphate is readily soluble in water at acidic pH. Chloroquine sulfate is soluble in a mixture of water and methanol but non-soluble in pure water. The drug is sensitive to light and should be protected from light. The molecular weights of the base, phosphate, sulfate, and hydrochloride salts are 320, 516, 436, and 393, respectively. Structure-activity relationship (SAR) studies of many derivatives of the 4-aminoquinolines show that halogen substitutions at any position other than seven reduce pharmacologic activity and toxicity. An aryl rather than an alkyl side chain decreases the therapeutic ratio. Increasing alkyl side chain length above five carbons decreases the therapeutic ratio and increases toxicity.

Pharmacological Activities

Antimalarial Activity and Mechanism of Action and Resistance Chloroquine is highly effective and acts rapidly against asexual erythrocytic forms of *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, *Plasmodium knowlesi*, and chloroquine-sensitive *P. falciparum.* (−)-Chloroquine is less active than (+)-chloroquine enantiomer against chloroquine-resistant strains of *P. falciparum*. Chloroquine is also active against gametocytes of *P. vivax*, *P. malariae*, and *P. ovale* and immature forms of *P. falciparum.* The drug has no effect against the exoerythrocytic tissue stages of malaria. Its major plasma metabolite monodesethylchloroquine (Fig. 1b) has similar antimalarial activity against chloroquine-susceptible parasites in vitro, but it is less effective than the parent compound against chloroquine-resistant strains.

The mechanisms of action and resistance of chloroquine have not been fully elucidated. Proposed mechanism(s) of action include DNA binding, inhibition of various enzymes (e.g., mixed-function oxidase, heme polymerase, phospholipase, and glutathione-S-transferase) and/or transporters, inhibition of protein synthesis, interference with digestion of host-derived hemoglobin in the parasite digestive food vacuole (acid lysosome), and lysosomotropic effect. Interference with hemoglobin digestion process and alteration of lysosomal pH appear to be important mechanisms of chloroquine action. During the process of hemoglobin digestion, the protein moiety of hemoglobin is degraded to related peptides, and heme is transformed into hemozoin (HZ), a nontoxic crystalline polymer. Chloroquine is a weak base with pKa values of 8.1 and 10.2 and the protonation of the drug encharged at the neutral pH of the blood. With the acidic pH for parasite food vacuole, chloroquine accumulates and binds hematin, a toxic product of hemoglobin degradation, therefore preventing its incorporation into the hemozoin crystal. The free hematin interferes with the parasite detoxification processes and thereby damages the *Plasmodium* membranes by lipid peroxidation mechanism.

Resistance to chloroquine in *P. falciparum* involves mainly the mutation in the parasite transport gene *pfcrt* (*Plasmodium falciparum* chloroquine resistance transporter) along with *pfmdr1* (*Plasmodium falciparum* multidrug resistance 1) and *pfmrp1* (*Plasmodium falciparum* multidrug resistance-related protein 1). The *pfcrt* gene is located on chromosome 7 and encodes a 49 kDa protein (PfCRT) localized in parasite's food vacuole with ten predicted transmembrane domains.

An amino acid substitution at position 76 from lysine to threonine (K76 T), located on the first transmembrane domain, has been reported to be directly associated with chloroquine-resistant *P. falciparum* isolates in wide geographic areas. The *pfmdr1* gene is located on chromosome 5 and encodes a homologue of the mammalian multidrug resistance gene in *P. falciparum*, P-glycoprotein homologue 1 (Pgh-1). *Pfmdr1* can modulate the degree of chloroquine resistance in some parasite strains, suggesting that some alleles and overexpression of PfMDR1 may enhance chloroquine concentration within the digestive food vacuole by active transport. The *pfmrp1* is located on chromosome 1 and encodes a 1822 amino acid proteins PfMRP1 which is a transporter member of the ATP-binding cassette (ABC) proteins similarly to PfMDR1. It is localized to the parasite plasma membrane. PfMRP1 modifies drug responses but is not a major determinant of chloroquine resistance. Potential inhibitors of these parasite transport proteins which could effectively reverse chloroquine-resistant *P. falciparum* in clinical settings are being investigated.

Other Pharmacological Activities and Clinical Uses Apart from malaria, chloroquine is commonly used in patients with several inflammatory conditions, such as rheumatoid arthritis, systemic lupus erythematosus (SLE), discoid lupus erythematosus, porphyria cutanea tarda, polymorphous light eruptions, solar urticaria, recurrent basal cell carcinoma of the skin, porphyria cutanea tarda, and antiphospholipid antibody syndrome. In the treatment of amoebic liver abscess, chloroquine may be used instead of, or in addition to, other medications in case of unsatisfactory treatment efficacy or intolerance following metronidazole or another nitroimidazole within 5 days, as well as in case of intolerance to metronidazole or a nitroimidazole. The mechanism of action may involve its inhibitory effect on pro-inflammatory cytokine release into human whole blood. This effect may be of therapeutic benefit not only during chronic inflammation but also in diseases that are related to infection-induced inflammation.

Chloroquine has potential for use as an adjunct therapy with standard antiretroviral drugs. Synergistic activities have been demonstrated when chloroquine is used in combination with zidovudine, didanosine, and the protease inhibitors (indinavir, ritonavir, and saquinavir). Chloroquine is associated with low levels of HIV RNA in breast milk of the HIV-infected patients. In addition to HIV, inhibitory activity against the replication of severe acute respiratory syndrome (SARS) or coronavirus infections is shown in vitro.

Chloroquine also has potential for use as a chemosensitizer in cancer in conjunction with some conventional anticancer drugs, through inhibition of the function of membrane-associated proteins belonging to the P-glycoprotein and multidrug resistance (MDR) protein families.

Chloroquine is a potent autophagic drug that may lead to cellular degradation of hepatocytes in the liver with the concurrent production of vacuoles.

Chloroquine has been shown to inhibit glucose 6-phosphate dehydrogenase activity in vitro. Administration of chloroquine to rats also caused alterations in several hepatic and renal antioxidant enzymes, thereby inducing an oxidative stress in these organs.

Therapeutic Indications for Malaria

Chloroquine is one of the most successful and widely used medications and with obvious health precautions, saving countless lives from malaria since the 1940s. The drug was for several decades the antimalarial of choice because it was effective, well tolerable, safe, and low cost. However, its usefulness has rapidly declined in most malaria-endemic areas of the world where chloroquine-resistant strains of *P. falciparum* and *P. vivax* have emerged and widespread. *P. falciparum* chloroquine resistance was first suspected in the late 1950s and confirmed in 1959 in Thailand. Almost simultaneously, resistance occurred in an independent focus in Colombia and South America. The use of chloroquine for treatment of *P. falciparum* infection is currently restricted to few countries in Caribbean and Central America, and the World Health Organization (WHO)

strongly recommends artemisinin-based combination therapies (ACTs) for all *P. falciparum* confirmed cases in all endemic areas. Nevertheless, an increase in chloroquine susceptibility has been reported after withdrawal of the drug as first-line treatment, indicating that in the absence of the drug pressure, it is possible to restore chloroquine efficacy. The efficacy of chloroquine in the treatment of *P. vivax* and other non-*P. falciparum* is however still very high in most areas of the world including Thailand. Chloroquine-resistant *P. vivax* was first reported from Papua New Guinea in 1989, almost 30 years after the emergence of *P. falciparum* resistance. It is now widespread and has rendered this drug ineffective in parts of Indonesia and Papua New Guinea. Low levels of resistance have also been reported from Myanmar, South Korea, Vietnam, India, Turkey, Ethiopia, and parts of southern Africa and South America. Currently, chloroquine (or ACTs) is a therapeutic option for the treatment of adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae*, or *P. knowlesi* in areas with chloroquine-sensitive infections. Its use in combination, or not, with primaquine, the unique antimalarial drug that acts against the *Plasmodium* liver stage preventing relapses, is the first choice in the majority of endemic areas of these non-*P. falciparum* infections. Oral chloroquine is given at an initial dose of 10 mg/kg body weight (bw), followed by 10 mg/kg bw on the second day and 5 mg/kg bw on the third day (total dose of 25 mg/kg bw). In the past, the initial 10 mg/kg bw dose was followed by 5 mg/kg bw at 6, 24, and 48 h. Chloroquine phosphate is available orally as tablets containing either 250 or 500 mg of the phosphate (equivalent to 150 and 300 mg of base, respectively).

Chloroquine has been considered safe when used in normal therapeutic doses during pregnancy. No abortifacient or teratogenic effects have been reported.

Adverse Reactions and Toxicity

At therapeutic doses, chloroquine is generally well tolerated. Individual variations in the pattern of distribution of chloroquine and its metabolite in the body are suspected to play an important bearing on the incidence and pattern of adverse reactions to the drug. Large doses used for the treatment of rheumatoid arthritis are associated with a higher frequency of adverse reactions than the lower doses used in malaria. The main adverse reactions reported after therapeutic or prophylactic regimens include abdominal discomfort (nausea, vomiting, and diarrhea), headache, blurred vision, light-headedness, and fatigue. Gastrointestinal disturbance can be minimized by taking the drug with food. Ocular toxicity observed in chloroquine treatment is associated with disruption of the blood-retinal barrier (BRB). Serious adverse effect associated with long-term use of chloroquine, either as prophylaxis or treatment of rheumatoid arthritis, is irreversible retinopathy (0.3–2% incidence). Pruritus especially of the palms and soles occurs frequently in Africans. Rare adverse reactions are photosensitization, aplastic anemia, agranulocytosis, hepatitis, elevated liver enzymes, skin eruptions, psychiatric disturbances, peripheral neuropathy, myopathy, and effect on neuromuscular transmission (muscle weakness). There is some evidence that the drug may induce an autoimmune disorder particularly with long-term high-dose therapy. Several patients with autoimmune diseases (rheumatoid arthritis and SLE) developed clinical, physiological, and pharmacological evidence for myasthenia gravis after prolonged use of chloroquine. Chloroquine may affect kidney function when taken either during treatment or prophylaxis of malaria through accumulation in adrenal gland and the epithelial cells of the kidney. Chronic administration of chloroquine has been reported to cause Na + retention possibly via increase in plasma aldosterone concentrations and renal Na+ -K+ -ATPase activity. The S(−)chloroquine is more toxic in humans than R(+) chloroquine.

Transiently high plasma chloroquine concentrations after the rapid intravenous injection or large intramuscular doses of chloroquine (previously used for treatment of chloroquine-sensitive severe *P. falciparum* malaria) are associated with cardiovascular toxicity. Toxic manifestations appear rapidly within 1–3 h after injection and include circulatory arrest, shock, cardiac conduction

disturbances, and ventricular arrhythmia. Abnormalities in the electrocardiogram (ECG), i.e., QRS complex widening, flattening of the QRS, and ST segment depression, have been reported after overdoses as well as in patients after therapeutic doses. Respiratory depression can also occur.

Contraindications

Chloroquine is contraindicated in individuals with known hypersensitivity to chloroquine or structurally related aminoquinoline antimalarials.

Caution

Chloroquine may exacerbate the severity of psoriasis, neurological (e.g., epilepsy) and gastrointestinal disorders, and retinal, visual, or hepatic impairment. The drug should be administered in patients with these underlying conditions with caution.

Pharmacokinetics

Pharmacokinetic parameters of chloroquine and its active plasma metabolite monodesethylchloroquine following currently recommended doses for malaria treatment and prophylaxis are summarized in Table 1. Chloroquine is rapidly and almost completely absorbed from the gastrointestinal tract after oral administration in either healthy subjects or children with malaria. The oral bioavailability is almost complete, i.e., approximately 90%. Absorption is relatively unaffected by concomitant ingestion of food. However, intersubject variability of 30–100% has been reported in extent of absorption, which may explain in part the individual variability of chloroquine effectiveness and toxicity. In one study following a single oral dose of 300 mg chloroquine base, peak plasma chloroquine levels of 56–102 ng/ml were attained within 1–6 h. In another study where 10 mg chloroquine per kg body bw was administered in the form of tablets to children with malaria, a C_{max} of about 250 ng/ml was reached in 2 h with an absorption half-life of 0.56 h. Multiple doses of 250 mg daily lead to stable plasma concentrations of 100–500 ng/ml.

The pharmacokinetics of chloroquine is complex with plasma levels determined by the rate of distribution rather than by the rate of elimination. In systemic circulation, about 50–70% of chloroquine is bound to plasma protein, mainly to α_1-acid glycoprotein. S(+)Chloroquine binds more to albumin (50%) than R(−)chloroquine (35%). On the other hand, R(−)chloroquine binds more to α_1-acid glycoprotein (48%) than S(+)chloroquine(35%). Chloroquine is extensively distributed throughout the body. The drug is deposited in tissues (liver, spleen, kidney, lung, retina, and skin) with about 200–20,000 times the plasma concentration. Highest concentrations of chloroquine are found in melanin-containing cells in the retina and skin. The drug remains in the skin for 6–7 months after cessation of therapy at a time when the drug is no longer detectable in the plasma. The extent of accumulation of the R(−) chloroquine in ocular tissues is greater than that of the S(+) enantiomer. Chloroquine readily crosses the placenta and is excreted in small amount into the breast milk. The milk-to-plasma ratio ranges from 1.96 to 4.26. Cord blood concentration is similar to maternal blood level. Correlation is observed between saliva and plasma levels of chloroquine with saliva: plasma concentration ratio of 0.53. Due to its extensive tissue distribution (Vc/F), the apparent volume of distribution (Vd/F) is extremely large (31–262 l/kg), but the volume of the central compartment is relatively small. This results in transiently high plasma chloroquine concentrations after parenteral administration with wide peak-to-trough fluctuations.

The distribution of chloroquine within the human blood is also important since the malaria parasite is intraerythrocytic during schizogony. Chloroquine preferentially concentrates in blood components, e.g., erythrocytes, platelets, and granulocytes. Erythrocytic concentration is about two to five times of the concurrent plasma concentrations. Concentration in parasitized erythrocytes is about 25 times of normal erythrocytes. Concentration in the whole blood is highest, followed by serum and plasma. It is thought that chloroquine-induced redistribution of a neutral aminopeptidase may be the cause of hemoglobin accumulation in endocytic vesicles of malaria parasites.

Clearance of chloroquine is mainly by renal excretion (40–70%) and hepatic metabolism

Pharmacology of Antimalarial Drugs, Current Anti-malarials, Table 1 Pharmacokinetic parameters of antimalarial drugs and their active metabolites in studies in healthy subjects and patients with malaria. Data are presented as range of mean or median values reported (World Health Organization, Division of Control of Tropical Diseases. Guidelines for the treatment of malaria. Third edition, 2015)

	Pharmacokinetic parameters					
Drug/metabolite	C_{max} (ng/ml)	T_{max} (h)	AUC (ng.h/ml)	CL/F (l/h/kg)	Vd/F (l/kg)	$T_{1/2}$ (h)
Amodiaquine Desethylamodiaquine	5.2–39.3 161–751	0.5–2.0 2.71–47.9	39.3–602 14,700–-40,339	14–57.8 0.61–0.74	311–1010 62.4–252	3.3–12.4 90–240
Artemether Dihydroartemisinin	171–540 15–405	1.5–10.0 1.3–7.4	810–5800 190–5040	0.44–138 (CL) 7.16–8.99 (CL)	3.5–8.6 (Vd) 2.05 (Vd)	5.7–7.0 5.1
Artemether Dihydroartemisinin Lumefantrine Desbutyllumefantrine	5.2–190 26–205 4456–28,300 19.3–89.0	0.5–2.13 0.8–3.0 2.0–66.3 8.0–62.7	40–385 90–382 207,000–2,730,000 5400	1.46–41.26 3.48–13.61 0.077–0.104 10.0	9.85–143.5 1.038–35.6 0.4–8.9 730–977	0.5–2.13 0.8–3.0 2–66.3 8.062.7
Artesunate (iv) Dihydroartemisinin	1140–29,644 340–3007	2 9–17.4	505,000–2,051,000 1,107,000–2,559,000	1.27–3.12 (CL) 0.73–2.16 (CL)	0.08–0.24 (Vd) 0.75–2.22 (Vd)	9–25.2 20.7–95.4
Artesunate (im) Dihydroartemisinin	660–2192 62.5–1584	8 1.4–40.5	855,000 1,496,000	2.7–4.26 (CL) 1.08–1.21 (CL)	0.44–2.16 (Vd) 0.77–1.79 (Vd)	11.5–48.2 32–52.7
Artesunate (rectal) Dihydroartemisinin	90–894 180–1279	42–54 12–138	692,000 2,402,000–2,786,000	5.9 1.5–2.64	2.06 0.6–2.8	51 18–81
Artesunate (oral) Dihydroartemisinin	34–451 900–2043	30–84 54–120	113–419 1,217,000–3,745,000	0.61–15.4 0.63–1.66	0.63–3.35 1.45–3.00	54 48–150
Atovaquone Proguanil Cycloguanil	634–13,270 560–751 37–67	5.1–5.7 4.4–5.2 6.4–6.9	2.67–27.63 ug.days/ml 7200–15,400 600–1800	90–320 710–1230 –	4.7–13 13.4–22.9 –	29–134 8.0–17.6 15.6–22.6
Chloroquine Desethylchloroquine	283–1430 89–220	2.7–6.9 –	8200–140,000 23,100–64,300	0.23–0.80 0.1–0.16	31.8–262 12.6	108–291 175–290
Dihydroartemisinin Piperaquine	366–698 71.6–730	0.97–2.8 1.48–5.7	0.84–1.95 24,100–49,500	1.19–2.16 0.85–1.85	1.47–3.59 529–877	0.85–1.40 13.5–28 days
Doxycycline	3060–6900	1.5–6.0	39,000–108,400	29.5–112.0	0.75–1.83	8.8–22.4
Mefloquine (treatment)	1000–3279	15–72	12.8–63.6 ug.days/ml	0.016–0.174	7.87–31.8	8.1–15.2 days
Mefloquine (prophylaxis)	722–2259	4.5–31	15.6–48.0 ug.days/ml	0.016–0.095	10.11–14.60	1.03–19.1 days
Primaquine Carboxyprimaquine	65–295 343–2409	1.8–4.0 4–8	443–1978 3831–47,085	0.31–1.19 –	2.92–7.94 –	3.5–8.0 15.7–16.9
Quinine	5270–17,900	1.0–5.9	9200–449,000	0.22–4.99 (CL)	0.45–4.24 (Vd)	3.21–26.0
Sulfadoxine	57,900–217,800	3.7–63	15,900–66,300	13.9–71.1 ml/day/kg	0.263–0.660	4.1–10.9
Pyrimethamine	86,000–860,000	2.4–41.1	21,787–106,065	335–1776 ml/h/kg	2.32–7.20	60–450
Pyronaridine	491–1816	1.3–1.7	16,300–42,500	0.55–1.25	39–105	147–242.6

(35–50%). Hepatic metabolism is largely by side chain de-ethylation, leading first to monodesethylchloroquine (30–40%) and then to didesethychloroquine or bisdesethylchloroquine (5–10). Monodesethylchloroquine (Fig. 1b) is the main metabolite of chloroquine with similar antimalarial activity against chloroquine-susceptible *P. falciparum* as the parent compound. Bisdesethylchloroquine is further deaminated to form an alcohol (the 4'-hydroxy compound) which is oxidized to the 4'-carboxylic acid derivative. Successive dealkylation of the side chain ultimately produces the compounds 7-chloro-4-aminoquinoquinoline, chloroquine side chain *N*-oxide, and chloroquine di-*N*-oxide. Metabolism of chloroquine involves the cytochrome P450 (CYP450) system, i.e., CYP2C8, CYP3A4/5, and, to a much lesser extent, CYP2D6, although their quantitative in vivo contribution remains unclear. All the metabolites are toxicologically important. Metabolism of chloroquine occurs slowly, and the main metabolite varies in different species. Extrahepatic sites of microsomal metabolism could also be of clinical significance in view of the extensive tissue distribution of chloroquine and the extrahepatic distribution of CYP3A isoenzymes.

The monodesethylchloroquine metabolite has similar profiles of distribution and tissue binding as the parent drug and can be detected in plasma 30 min after drug administration. Time to maximum blood concentration (t_{max}) of 2–7 h after the oral dose occurs at approximately the same time as that of chloroquine. The binding of monodesethylchloroquine to α_1-acid glycoprotein is higher than that to albumin (21% vs 3%). The concentration of monodesethylchloroquine remains at a value of 25–40% of that of the parent compound after the peak has been reached. At steady state, the ratio of chloroquine to desethylchloroquine is 6–10%. Bisdesethylchloroquine concentration reaches 10–13% of chloroquine concentration.

Chloroquine exhibits a multiexponential elimination pattern with a more rapid initial elimination phase, followed by a slower phase. The systemic clearance of chloroquine (CL/F) varies between 0.23 and 0.80 l/h/kg. Renal clearance accounts for up to 70% of the total systemic clearance by both glomerular filtration and tubular secretion, in the forms of unchanged (about 50%) or metabolized drugs (25%). The excretion is increased by acidification of the urine. The S(+) enantiomer is excreted by the kidneys preferentially compared to the R(−) enantiomer. Approximately 8–25% and 5% are excreted in unchanged form or metabolites in the feces and skin, respectively. About 25–45% is stored long term in lean body tissues. The reported values of $t_{1/2}$ of chloroquine and metabolite vary considerably, depending largely on the duration of sampling and the analytical methods used, i.e., 2.5 and 10–60 days for 7 days and >56 days sampling, respectively. The elimination half-lives ($t_{1/2}$) of chloroquine, mondesethylchloroquine, and bisdesethylchloroquine range from 20 to 60 days. The $t_{1/2}$ of the modesethyl metabolite is longer than those of the parent compounds. Chloroquine and metabolites can be found in urine for months after a single oral dose.

Factors Associated with Altered Drug Exposure and/or Treatment Response

Various pharmacokinetic studies suggest noticeable interindividual variability in chloroquine and monodesethylchloroquine concentrations, and this variability may influence the parasitological treatment outcome. In most cases, blood/plasma concentrations in patients with treatment failure tended to be lower than those with sensitive treatment outcome. In addition, this variability may also associated with increased chloroquine toxicity particularly retinopathy.

Malaria Infection There appears to be no pharmacokinetic difference of chloroquine, besides the higher C_{max} found in Thai patients with malaria compared with healthy subjects following an intravenous infusion of chloroquine diphosphate (15 mg base/kg bw). The binding of chloroquine to plasma protein is not altered in malaria infection.

Pregnancy The CL/F and Vd/F of chloroquine may be increased, while area under blood concentration-time curve (AUC) decreased in pregnant patients. Decreases of 25% and 45% in

the AUCs of chloroquine and desethylchloroquine, respectively, suggest lower exposure that may compromise therapeutic efficacy. Recommendation to increase chloroquine daily dose to four tablets (1,000 mg) regimen in pregnant women is proposed based on results of a population-based pharmacokinetic study to improve clinical efficacy of chloroquine. Clinical studies evaluating safety and potential harm to the fetus are needed. Data on the use of antimalarials by lactating mothers have been limited.

Children and Elderly Information on the influence of age on the pharmacokinetics of chloroquine has been limited. It has only been recognized recently that the currently recommended on the mg *per* kg bw doses of chloroquine achieve substantially lower plasma drug concentrations in young children than in older patients.

Renal Diseases Kidney or liver dysfunction decreases excretion of chloroquine and leads to greater drug retention and higher risk of chloroquine toxicity. In patients with renal insufficiency, chloroquine elimination is reduced resulting in the prolongation of the $t_{1/2}$ of the drug. Blood concentrations at equilibrium level of chloroquine are about 70% higher in patients with renal impairment. However, this pharmacokinetic alteration is of therapeutic relevance only when chloroquine is used for prophylaxis but not for treatment, as the concentration-time profiles of chloroquine are largely governed by distribution phase rather than elimination phase during the first 3–4 days acute phase of infection.

Malnutrition In malnourished patients, the metabolism of chloroquine is impaired and may result in high blood concentrations.

Ethnics In general, the pharmacokinetics of chloroquine does not differ substantially in different ethnic groups. However, in one study, the rate of chloroquine excretion of during the first 7 h of administration was higher in Thais as compared to British, Gambian, and Sudanese subjects. The proportions of excreted monodesethylchloroquine to chloroquine were similar in all groups.

Genetic Polymorphisms in Drug-Metabolizing Enzymes and Transporters The role of polymorphisms of CYP2C8, the key enzyme in chloroquine biotransformation, as a factor that influences treatment outcome has not yet been investigated. It is, however, unlikely to be clinically relevant since both parent compound and metabolite are pharmacologically active. The contribution of polymorphism in protein transporters particularly regarding chloroquine-induced adverse drug effects of the central nervous system (CNS) remains to be clarified.

Drug Interactions There is evidence from in vitro and in vivo animal studies that chloroquine is markedly antagonistic to some antimalarials such as quinine, mefloquine, amodiaquine, and artemisinin. On the other hand, the combination with sulfadoxine, pyrimethamine, and erythromycin is synergistic. Clinical relevance for the interaction of chloroquine with some of these drugs has been demonstrated. In clinical situation where concomitant therapy of chloroquine with other antimalarials cannot be avoided, monitoring of chloroquine blood concentrations is suggested. Despite the encouraging results for the synergistic effects of the combination of chloroquine and erythromycin in vitro and in vivo, the combination of chloroquine and erythromycin does not prove effective in the treatment of highly chloroquine-resistant *P. falciparum* in Thailand or even less chloroquine-resistant parasites in Kenya. Desferrioxamine, the only iron chelator used in human medicine, has been shown to inhibit *P. falciparum* growth both in vitro and in an animal model. However, marked antagonism is observed between desferrioxamine and chloroquine.

Calcium channel blockers, tricyclic antidepressants, and antihistamines inhibit chloroquine transport by P-glycoprotein resulting in increased blood chloroquine levels and antimalarial activity. The antihistamine cyproheptadine has been shown to reverse resistance to chloroquine in *P. falciparum* both in vivo and in vitro.

Food appears to enhance the extent of chloroquine absorption. The AUC and C_{max} of chloroquine are significantly elevated when chloroquine

was administered with rice-based meals, although the rate of absorption is not affected.

In animal studies, acetylsalicylic acid delayed the absorption of chloroquine, but distribution, plasma protein binding, and elimination were not affected. Clinical relevance of these findings remains to be established.

Concomitant therapy of chloroquine with some antacids or antidiarrheal agents results in poor bioavailability of chloroquine.

Activated dimethicone does not appreciably affect the absorption of chloroquine, but calcium carbonate, kaolin, and magnesium trisilicate significantly decrease the absorption of chloroquine.

Activated charcoal has been shown to drastically reduce the absorption of chloroquine. The plasma AUC and C_{max} of chloroquine were reduced by 99% in the presence of activated charcoal. Activated charcoal should have a role in reducing the absorption in chloroquine intoxication.

The co-administration of primaquine with chloroquine for radical treatment of *P. vivax* malaria does not affect chloroquine or monodesethylchloroquine pharmacokinetics but significantly increases plasma primaquine concentrations. This pharmacokinetic interaction may explain previous observations of synergy in preventing *P. vivax* relapse. Similarly, non-clinically significant safety or pharmacokinetic/pharmacodynamic interactions are found with the co-administration of tafenoquine (antirelapse drug alternative to primaquine) and chloroquine in healthy subjects.

Cimetidine, but not ranitidine, impairs the elimination of chloroquine through inhibition of drug-metabolizing enzymes. Ranitidine is, therefore, the H_2-receptor antagonist of choice for ulcer patients receiving chloroquine therapy. Plasma concentration of chloroquine is also increased when co-administered with paracetamol.

Alkalinization of urine decreases chloroquine excretion. Acidification of the urine by oral ingestion of ammonium chloride can increase renal excretion of chloroquine by 20–80%. Intramuscular injection of dimercaprol can also increase urinary excretion of chloroquine.

Chloroquine has been shown to reduce bioavailability of ampicillin, praziquantel, and methotrexate, as well as reduce therapeutic effect of thyroxine. On the other hand, the drug increases plasma concentration of cyclosporine.

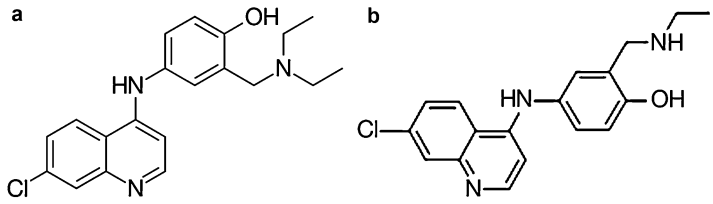
Concurrent administration of chloroquine and ethanol has been shown to induce extensive damage to the proximal tubules and collective duct cells of the kidney, probably due to modulatory effect of chloroquine on the renal tubular response to vasopressin, either directly by inhibiting cyclic AMP generation or indirectly via induction of nitric oxide production.

Amodiaquine

Amodiaquine is an analog of chloroquine, which is effective against low-level chloroquine-resistant *P. falciparum* malaria. In the 1980s, the use of amodiaquine was discouraged due to rare but serious idiosyncratic hepatotoxicity and agranulocytosis after long-term prophylaxis. In the 1990s, its use was reconsidered following the widespread development of chloroquine resistance. It is now recommended by WHO to be used in combination with artesunate as one of the artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated *P. falciparum* and *P. vivax* in areas where the parasites are sensitive to amodiaquine. Recently, *WHO has recommended seasonal malaria chemoprevention (SMC) using a complete treatment of sulfadoxine-pyrimethamine and amodiaquine once a month for 4 months during the malaria transmission season for children aged between 3 and 59 months.*

Chemistry and Physical Properties

Amodiaquine (4-[(7-Chloroquinolin-4-yl)amino]-2-[(diethylamino)methyl]phenol: Fig. 2a) is a Mannich base 4-aminoquinoline that is similar in chemical structure and mechanism of action to chloroquine. Amodiaquine is a yellow crystalline powder, odorless (or almost odorless) with a bitter taste. Soluble 1 in 22 parts water 1 in 70 parts ethanol (96%). The molecular weight is 355.9. Amodiaquine is practically insoluble in benzene, chloroform, and ether. It is decomposed at temperature 150–160 °C. The drug is used as a racemic mixture of equal amounts of S(+) and R(−) amodiaquine.



Pharmacology of Antimalarial Drugs, Current Anti-malarials, Fig. 2 Chemical structures of (**a**) amodiaquine and (**b**) monodesethylamodiaquine

Pharmacological Activities

Antimalarial Activity and Mechanism of Action and Resistance Amodiaquine has antimalarial activity on various *Plasmodium* stages similarly to that of chloroquine. It is active against asexual erythrocytic forms of *P. vivax*, *P. ovale*, *P. malariae*, *P. knowlesi*, and chloroquine-sensitive *P. falciparum.* It is also active against gametocytes of *P. vivax*, *P. malariae*, *P. ovale*, and immature forms of *P. falciparum.* The drug has no activity against the exoerythrocytic tissue stages of malaria. Its major plasma metabolite monodesethylamodiaquine (Fig. 2b) has similar antimalarial activity. The mechanisms of action and resistance of amodiaquine have not been fully elucidated but are thought to be similar to chloroquine.

Therapeutic Indications for Malaria

Oral amodiaquine is currently available as a single tablet and a fixed-dose combination (ACT) in tablets containing 25/67.5 mg, 50/135 mg, or 100/270 mg of artesunate-amodiaquine. Amodiaquine in combination with artesunate as one of the ACTs is indicated for the treatment of uncomplicated *P. falciparum* and *P. vivax* malaria. The combination is also active against *P. vivax*, *P. ovale*, *P. knowlesi*, and *P. malariae.* The recommended dose regimen for ACT is a total therapeutic dose range of 6–30 mg/kg bw *per* day artesunate and 22.5–45 mg/kg bw *per* day amodiaquine for 3 days. The combination may also be used as follow-on treatment in patients with severe malaria if oral medication is tolerated. In areas with high malaria transmission in the sub-Sahel region of Africa where the majority (>60%) of clinical malaria cases occur during a short period (≤4 months), seasonal malaria chemoprevention (SMC) with monthly amodiaquine in combination with sulfadoxine-pyrimethamine is recommended for all children aged less than 6 years during each transmission season. The combination is given at full treatment doses, i.e., a single dose of sulfadoxine-pyrimethamine (25/12.5 mg) and 3 days of amodiaquine (10 mg/kg bw *per* day) at monthly intervals.

Adverse Reactions and Toxicity

The adverse reactions of amodiaquine are generally mild to moderate and are similar to chloroquine. Hepatic problems or decrease in blood counts may rarely occur. Toxicity from overdose may include headache, seizures, and cardiac arrest.

Artesunate-amodiaquine is generally well-tolerated. Common adverse reactions include gastrointestinal disturbances (nausea and abdominal pain), cough, anorexia, insomnia, fatigue, and weakness. The incidence of gastrointestinal disturbances is higher compared with other ACTs. Less common adverse reactions are arrhythmia, bradycardia, vomiting, extrapyramidal effects, retinopathy, and pruritus. Eye disorders (transient accommodation disorders and corneal opacification) varying in types and severity have also been reported but regress upon termination of treatment. Serious adverse reactions are neutropenia and hepatotoxicity. These serious effects are most often with prolonged use of amodiaquine for prophylaxis or prolonged use of artesunate-amodiaquine treatment.

Amodiaquine-SP is generally well tolerated in children. Common adverse reactions include vomiting, loss of appetite, fever, and mild-to-

moderate skin reactions. No serious adverse reactions have been reported.

Contraindications

Amodiaquine should not be administered to patients with known hypersensitivity to amodiaquine and structurally related drugs. In addition, clinical use with this drug should be avoided in patients with history of hepatotoxicity, hepatic impairment, neutropenia, or retinopathy.

Cautions

Although there is no evidence for life-threatening cardiovascular complications of amodiaquine as what has been reported with overdose of chloroquine, caution should be made in treating patients who have recently taken another antimalarial drug with cardiovascular adverse reactions such as quinine, mefloquine, or even chloroquine.

Pharmacokinetics

Pharmacokinetic parameters of amodiaquine and its active plasma metabolite following currently recommended doses for treatment of uncomplicated malaria and seasonal malaria chemoprevention are summarized in Table 1.

After oral administration, amodiaquine hydrochloride is rapidly absorbed and undergoes rapid and extensive metabolism by CYP2C8 to the active metabolite monodesethylamodiaquine (Fig. 2b) and the secondary metabolite 2-hydroxyamodiaquine which are eliminated by renal excretion. Monodesethylamodiaquine is concentrated in red blood cells; whole blood to plasma ratio is approximately 3:1. Both the parent drug and metabolite are highly (>90%) plasma protein bound. It is likely that the distribution of monodesethylamodiaquine in man mirrors that of chloroquine, i.e., wide distribution into the body tissues, particularly in the liver, spleen, kidney, lungs, brain, and spinal cord. It also binds to melanin-containing cells in the eyes and skin. Although amodiaquine is three times more potent than monodesethylamodiaquine, monodesethylamodiaquine remains longer in blood where it concentrates in red blood cells and is claimed responsible for the most of the antimalarial efficacy of amodiaquine. Blood concentrations of amodiaquine and monodesethylamodiaquine show wide (more than ten times) variation between individuals.

Factors Associated with Altered Drug Exposure and/or Treatment Response

Malaria Infection The oral pharmacokinetic profiles of amodiaquine and monodesethylamodiaquine obtained from patients with malaria and healthy subjects are similar, except the absorption which is significantly delayed in patients from a mean of 0.5–1.75 h.

Children Small studies did not find any effect of age on plasma concentrations of monodesethylamodiaquine or amodiaquine itself. However, it was reported that treatment failure after amodiaquine monotherapy was more frequent among children who were underweight for their age.

Pregnancy There are no data published on the pharmacokinetics of amodiaquine in pregnant women although it was previously used to treat malaria in pregnancy.

HIV Coinfection Artesunate-amodiaquine combination is associated with severe neutropenia, particularly in patients coinfected with HIV and especially in those on zidovudine and/or cotrimoxazole treatment. Concomitant use of efavirenz increases exposure to amodiaquine and hepatotoxicity. Concomitant use of this ACT with these drugs should therefore be avoided.

Genetic Polymorphisms in Drug-Metabolizing Enzymes Enzymatic and nonenzymatic formation of highly reactive amodiaquinequinoneimine, a protein-arylating intermediate, is thought to be responsible for serious organ-damaging amodiaquine adverse reactions observed in some patients. The effects of CYP2C8 polymorphisms on amodiaquine efficacy and toxicity remain conflicting. Theoretically, a slower conversion of amodiaquine to monodesethylamodiaquine in the CYP2C8 poor metabolizers might predispose patients to form this highly reactive intermediates

and, thus, increased risk of toxicity. The pharmacological activity of both amodiaquine and monodesethylamodiaquine, their antiparasitic synergism, or their extrahepatic metabolism might have hidden a CYP2C8 poor metabolizer phenotype and prevented treatment failure.

Drug Interactions Amodiaquine has potential to inhibit CYP2D6 and CYP2C9 activities. On the other hand, amodiaquine metabolism may be inhibited by CYP2C8 and CYP2A6 inhibitors. Plasma concentration of chloroquine including CYP450 activities has been shown to be increased when co-administered with the anti-HIV efavirenz. On the other hand, the concentration is decreased when co-administered with nevirapine.

With regard to pharmacodynamic interactions, increased risk for cardiotoxic effects may occur if amodiaquine is co-administered with antiarrhythmic drugs. In addition, the risk for neutropenia may be increased when amodiaquine is co-administered with zidovudine-containing regimens and trimethoprim-sulfamethoxazole combination.

Primaquine

Primaquine was first synthesized as the most potent compound in a large series of quinoline derivatives in 1946, by Elderfield and colleagues at Columbia University, and was later on investigated in humans as part of the US government's Malaria Project conducted at the Stateville Penitentiary. The first mass use of primaquine was in the Korean War in over 250,000 US soldiers as a tissue schizonticide to eliminate long latency *P. vivax* infections with a 14-day primaquine course. Since then, primaquine has gradually become the standard therapy in treating relapsing malaria and an important tool in malaria transmission blocking (gametocytocidal activity) and elimination campaigns with high effectiveness. Its effectiveness has nevertheless always been challenged with availability, prescribing practices, and patients' compliance. Most importantly, hemolytic toxicity particularly in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency is of concern, which significantly decreases effectiveness of primaquine.

Chemistry and Physical Properties

Primaquine [8-(4-Amino-1-methylbutylamino)-6-methoxy-quinoline: Fig. 3a] is an 8-aminoquinoline antimalarial. Primaquine is a racemate with equal parts of S(+) and R(−) forms because of the presence of an asymmetric carbon atom. The molecular weights of the base and diphosphate salts are 259 and 455. The diphosphate is the commercially available salt. It is soluble in water, and its solutions are stable, although some decomposition may take place on exposure to light and air.

Pharmacological Activities

Antimalarial Activity Primaquine is highly active against exoerythrocytic forms (hypnozoites) and sexual stages (gametocytes) of all *Plasmodium* species. It has weak activity against asexual blood stages of *P. vivax* but has negligible activity against *P. falciparum.*

Primaquine is active against primary tissue stages in the liver of all human *Plasmodium* species and can be considered to be a causal prophylactic agent. However, due to its toxicity, it has not been used for this purpose on a large scale. It is the only compound available for clinical use in the treatment of hypnozoite tissue stages form of *P. vivax* and *P. ovale*, to prevent relapses of these two species. It is also the only active drug against mature gametocytes of *P. falciparum* and is used routinely in areas under active control of malaria transmission. Primaquine has no substantial effect on blood stage of human malaria unless toxic concentrations are achieved.

The exact mechanism of action of primaquine as anti-hypnozoite and gametocytocide remains unclear. The main mechanism is proposed to be through parasite metabolism in mitochondria, eventually by interference with the ubiquinone function as an electron carrier in the respiratory chain. Another potential mechanism is the production of highly reactive metabolites that generate intracellular oxidative potentials. Primaquine has been shown to bind to PfCRT and can thereby inhibit chloroquine transport. This may explain the synergistic action between the two animalarials as well as the reversal of chloroquine resistance. Biotransformation of primaquine

appears to be necessary for their toxicity as well as efficacy. Selective generation of oxidative stress in the parasitized cells is the most plausible mechanism for primaquine toxicity and efficacy. It is possible that primaquine may have two entirely different modes of action, one through the parent compound and another through its metabolite(s). Different metabolites exhibit a varying degree of antimalarial activity. However, it is still unclear whether these metabolites or the parent compound exert the most important antiparasitic action. Current knowledges suggest that the 4-amino-1-methyl side chain is important in antimalarial activity. The 5-hydroxydemethylprimaquine (formed by deamination and oxidation of primaquine) is the most active metabolite. Carboxyprimaquine is considerably less active than primaquine against exo-erythrocytic stages of *P. berghei* in vitro.

The resistance to primaquine is incredibly low. This may be associated with its physical, chemical, or biological properties, together with its short half-life and ability to sterilize the parasite's gametocytes. Relapses of *P. vivax* malaria shortly after primaquine therapy have been reported in the Western Pacific, Southeast Asia, India, and Central and South America. Nevertheless, the frequency, intensity, and distribution of those isolated reports do not appear alarming. Primaquine resistance is commonly confused as failure of therapy or inability to remove the hypnozoite liver stage of *P. vivax* after the full course of therapy and correct therapeutic dose. The other important factor in detection of therapy failure with primaquine is adherence to medication. The exact mechanism of resistance of primaquine has not been identified.

Other Pharmacological Activities and Clinical Uses Primaquine is useful for prophylaxis and treatment of moderate *Pneumocystis carinii* pneumonia (PCP) or as salvage therapy when given in combination with clindamycin. The drug interferes with the microbial electron transport system by producing quinone metabolites that generate superoxides in vivo. The effective daily dose for PCP treatment is 2 mg/kg bw of primaquine and 225 mg/kg bw of clindamycin. Lower doses are applied for prophylaxis.

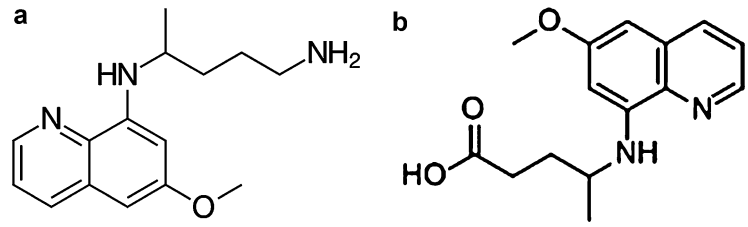
Primaquine has been shown to exhibit leishmanicidal activity in vitro but has no clinical application against leishmaniasis. Some derivatives of primaquine, particularly 6-desmethyl-8-aminoquinolines, have been generally more active in vitro than the parent drug against macrophage-contained leishmania.

Both primaquine and 2-methyl-PQ derivative have been reported to be almost four times as effective as the standard drug nifurtimox, against Chagas model disease in mice. This anti-trypanosomiasis activity of primaquine relies on the metabolic formation of free radicals that increase the oxidative stress in *T. cruzi.* The drug is, however, not clinically used for the therapy of Chagas disease.

Other biochemical and physiological activities of primaquine demonstrated by in vitro or in vivo studies include inhibition of vesicular transport and blocking of the calcium-release-activated current, blocking of the appearance of Ca^{2+}influx currents in response to Ca^{2+}store depletion, blocking of $Na^{+}$and K^{+}cardiac channels, and inhibition of diverse types of voltage-gated ionic channels, as well as acetylcholine (ACh) receptors.

Therapeutic Indications for Malaria

Primaquine is indicated for malaria on four different clinical uses: (i) radical cure in individuals infected with *P. vivax* or *P. ovale*; (ii) presumptive antirelapse therapy (terminal prophylaxis) for persons extensively exposed to *P. vivax* or *P. ovale*; (iii) reduction of onward transmission of *P. falciparum* malaria in programs to eliminate *P. falciparum* malaria and in areas threatened by resistance of *P. falciparum* to artemisinins; and (iv) primary prophylaxis against all species of malaria. For radical cure of *P. vivax* and *P. ovale* infections, the efficacy is highly dependent on the concurrent administration of an effective blood schizontocidal agent. Primaquine is not recommended for use as a single drug as it is not effective against erythrocytic forms of *Plasmodia*; the drug must be co-administered with blood schizonticides. Primaquine dosage is customarily expressed in terms of the base. Primaquine phosphate USP is supplied in tablets containing 7.5 and 15 mg of base.



Pharmacology of Antimalarial Drugs, Current Anti-malarials, Fig. 3 Chemical structures of (**a**) primaquine and (**b**) carboxyprimaquine

A 14-day course (0.25–0.5 mg/kg bw daily) of primaquine with blood schizonticide (chloroquine or an ACT) is strongly recommended in children and adult patients (except pregnant women, infants aged lower than 6 months, women breast-feeding infants aged less than 6 months, women breast-feeding older infants unless they are known not to be G6PD deficient, and patients with G6PD deficiency) with *P. vivax* or *P. ovale* in all transmission settings (except pregnant women, infants aged less than 6 months, and women breast-feeding infants aged less than 6 months) to prevent relapse. In patients with mild-to-moderate G6PD deficiency, primaquine base is given at 0.75 mg/kg bw once a week for 8 weeks, with close medical supervision during the first 3 weeks of treatment for potential primaquine-induced hemolysis. In patients with severe G6PD deficiency, risk-benefit assessment needs to be taken on an individual basis by experienced tropical medicine physicians. When G6PD status is not known and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment for the risks and benefits of adding primaquine. In pregnant women, primaquine should be given on the basis of G6PD status to prevent future relapse following chloroquine weekly prophylaxis (until delivery and breast-feeding are completed).

A single dose of 0.25 mg/kg bw primaquine with an ACT is currently recommended in patients with uncomplicated malaria in low-transmission areas (except pregnant women, infants aged less than 6 months, and women breast-feeding infants aged less than 6 months) to reduce diseases transmission without G6PD testing. The change in policy from the previously recommended dose of 0.75 mg/kg bw in 2010 to 0.25 mg/kg bw in 2015 was based partly on a WHO Evidence Review Group report summarizing published literatures. This recommendation is later on supported by evidence assessed from a systematic review which suggests that the lower single dose (0.1–0.25 mg/kgbw) of primaquine given with the goal of reducing transmission of *P. falciparum* is less likely to cause hemolytic effects in people with G6PD deficiency than the previous 0.75 mg/kg bw dose and that severe hemolytic events are not very common.

Adverse Reactions and Toxicity

Primaquine is generally well tolerated when the drug is administered in the usual therapeutic doses with minimal adverse reactions. Primaquine biotransformation plays an important role both its toxicity and antimalarial action and involves chiral recognition, even though exact mechanisms are not yet established.

The common adverse reactions include dose-related gastrointestinal discomfort (nausea, vomiting, diarrhea, and abdominal cramps) and dizziness. Abdominal distress from primaquine can be alleviated by antacids and by administering the drug with a meal. The less well-documented adverse reactions of primaquine are derangement of leukocyte levels, i.e., dose-dependent granulocytopenia or agranulocytosis, and effects on immune mechanisms. Other rare adverse effects include hypertension, arrhythmias and corrected QT (QTc) interval prolongation, and symptoms related to the central nervous system. The effects on human fetus are unknown, but the use of primaquine in pregnancy is not recommended due to hemolytic effects. Primaquine has been shown to be mutagenic in *Escherichia coli* and *Salmonella typhimurium* test systems.

The two major serious adverse effects of primaquine are the propensity to induce the

formation of methemoglobin and hemolytic episodes when erythrocytes with deficiency in G6PD are present. The severity of primaquine-induced hematoxicity is related to dose and degree of G6PD deficiency. Methemoglobinemia, a predictable dose-related adverse effect, occurs occasionally with therapeutic dosage but is much more common with a higher than therapeutic dosage. Several of primaquine metabolites, except carboxyprimaquine, have shown greater propensity to cause methemoglobin formation than primaquine itself. Acute intravascular hemolysis is by far the most serious toxic hazard of primaquine which restricts the wider use of the drug. It occurs as a consequence of oxidant stress in individuals with G6PD deficiency, an inherited X chromosome-linked trait. Primaquine-induced hemolysis is characterized by severe anemia, intravascular hemolysis with dark urine, and mild jaundice. Hemolysis appears usually on the second or third day of administration of primaquine and continues for 5–7 days. The hematocrit level drops to 30% between days 8 and 12 when about half of the red cells have been destroyed. Hemoglobinuria often accompanies the hemolysis; serum bilirubin rises to 50–90 μM, and slight jaundice may appear; Heinz bodies occur commonly at first but disappear as the hemolysis intensifies. The symptoms are related to the effect of the anemia. The hemolysis is normally self-limiting upon withdrawal of the drug. The degree of G6PD deficiency varies greatly ranging from moderate in Africans (African variant A) to very high in people of Mediterranean origin (Mediterranean variant B) and in population groups scattered throughout Asia (Asian variants). Several phenolic analogs of primaquine have been proposed to cause hemolytic effect, e.g., 5-hydroxyprimaquine, demethylprimaquine, and 5-hydroxydemethylprimaquine. It is still uncertain whether the major metabolite carboxyprimaquine contributes significantly to the toxicity of primaquine, although it does not cause methemoglobin formation in vitro. Carboxyprimaquine does not inhibit drug metabolism in vitro; however, inhibition of the formation of carboxyprimaquine could lead to serious adverse effects, i.e., hemolytic anemia or other unexpected toxicity due to the shift of the metabolic pathway to hydroxylated metabolites or other metabolites responsible for this effect.

Contraindications

Primaquine is contraindicated in patients with known hypersensitivity to primaquine and related compounds as well as in patients with severe G6PD deficiency or methemoglobinemia. Since primaquine crosses the placenta and may cause hemolysis in G6PD-deficient fetus, it is not recommended for use during pregnancy or during breast-feeding unless the G6PD status of the infant is known. Nonclinical data from studies conducted in bacteria and in animals treated with primaquine show evidence of gene mutations and chromosomal/DNA damage, teratogenicity, and injury to embryos and developing fetuses when primaquine is administered to pregnant animals.

Primaquine is also contraindicated for children under 4 years of age, and its administration requires a previous test for G6PD status.

Caution

Primaquine should not be given to subjects with concurrent treatment with potentially hemolytic drug or agents capable of depressing the myeloid elements of the bone marrow.

Different variants of G6PD deficiency are associated with significantly different risks for hemolysis. Decision to prescribe primaquine must be based on an assessment of the risks and benefits of using primaquine in patients with mild-to-moderate G6PD deficiency or when the G6PD status is unknown and G6PD testing is not available. If primaquine administration is considered, baseline hematocrit and hemoglobin levels must be investigated before treatment, and close hematological monitoring (e.g., at day 3 and 8) is required. Adequate medical support to manage hemolytic risk should be available. Due to the potential for QTc interval prolongation, electrocardiogram (ECG) should be monitored when primaquine is administered in patients with cardiac disease, long QTc syndrome, a history of ventricular arrhythmias, uncorrected hypokalemia and/or hypomagnesemia, or bradycardia (<50 bpm) and during concomitant administration with QTc interval prolonging agents.

Pharmacokinetics

Pharmacokinetic parameters of primaquine and its plasma metabolite carboxyprimaquine following currently recommended doses in healthy subjects and malaria patients are summarized in Table 1.

Absorption after oral administration is rapid and almost complete with bioavailability of about 96%. C_{max} is achieved within 1–4 h of dosing. Mean absorption half-life ($t_{1/2a}$) is 30 min. The concentration-time profiles in whole blood and in plasma are similar. Primaquine is distributed throughout the body. The Vd/F is in the range of 3–8 l/kg. About 75% of primaquine is bound to proteins. Red cell concentration is relatively high. The drug also crosses the placenta, but it is not extensively found in breast milk.

Primaquine is predominantly cleared by hepatic metabolism with renal elimination accounting for less than 1% of the administered dose over 24 h. The CL/F is approximately 0.3–1.2 l/h/kg bw. Hepatic clearance of primaquine is via two distinct pathways. Monoamine oxidase (MAO-A) biotransforms primaquine to the predominant but inactive metabolite carboxyprimaquine (Fig. 3b). Carboxyprimaquine is slowly eliminated and also further biotransformed via CYP2C19, CYP2D6, and CYP3A4, which generates the reactive intermediates responsible for antimalarial activities and methemoglobinemia and hemolytic toxicity, particularly the phenolic metabolite 5-hydroxyprimaquine. Carboxyprimaquine reaches plasma concentrations more than ten times higher than those of the parent compound (at approximately 4–8 h). It accumulates with daily dosing of primaquine. In animal studies in the isolated perfused rat liver preparation, the formation of the carboxy metabolite of primaquine was enantioselective. Stereoselective metabolism also plays a role in both antimalarial activity and toxicity. Both primaquine and carboxyprimaquine are excreted mainly via the biliary tract and can be found in feces within 24 h of administration. Primaquine itself is also excreted in urine. (−)R primaquine is cleared more extensively to carboxyprimaquine than the (+)S enantiomer. The $t_{1/2}$ of primaquine and carboxyprimaquine are approximately 3–8 and 15–17 h, respectively.

The pharmacokinetics of primaquine and carboxyprimaquine after oral administration in man are unaffected by dose size, within the clinically used dosage range. Primaquine does not inhibit or induce its own metabolism in man; multiple-dose studies indicate that primaquine does not accumulate in the plasma over the 14 days period of treatment. No significant concentrations of primaquine are found in the predose plasma samples taken prior to the daily doses of the drug.

Factors Associated with Altered Drug Exposure and/or Treatment Response

Malaria Infection A single oral dose of 45 mg primaquine is rapidly absorbed in patients with *P. vivax* or *P. falciparum* malaria. Acute *P. falciparum* infection is associated with a reduction in the CL/F of primaquine, while $t_{1/2}$ remained unaffected. This change in the oral clearance is possibly due to an impairment of the drug-metabolizing enzyme system and/or a reduction in the absorption across the gastrointestinal tract. The pharmacokinetics of primaquine appears to be unchanged in patients with *P. vivax* malaria.

G6PD Status The status of G6PD enzyme activity does not influence the pharmacokinetics of primaquine.

Ethnics Ethnic diversity of primaquine pharmacokinetics suggests potential heritability. In Koreans, the C_{max} of primaquine has been shown to be about five times higher and the carboxyprimaquine concentration about two to five times lower than in Indian and Thai populations. Different exposure has also been seen between Caucasian and Thai males.

Gender Conflicting results have been reported on the effects of gender on the disposition of primaquine. Some studies reported increased exposure and hence greater adverse reactions in women, while others reported no effect of gender.

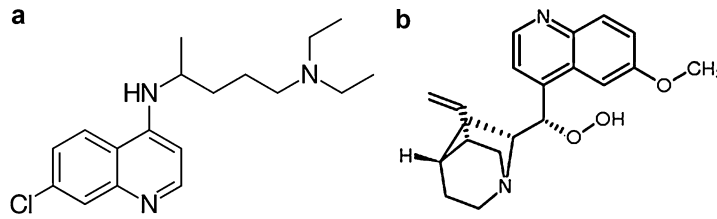
Renal Diseases The pharmacokinetics of a single oral dose of 15 mg primaquine does not appear to be altered in patients with severely impaired renal function and end-stage renal dysfunction.

Genetic Polymorphisms in Drug-Metabolizing Enzymes Genetic polymorphisms that decrease CYP2D6 enzyme activity reduce bioactivation of primaquine and may result in treatment failure. The treatment options for *P. vivax* infection in poor metabolizer are likely limited. Additionally, the use of primaquine as a prophylactic agent in this population would likely be ineffective. On the other hand, extensive metabolizers would likely be successful with primaquine therapy as they have the lowest parent primaquine levels and highest production of reactive metabolites and primaquine. Individuals with ultrarapid metabolizers would be expected to display the most primaquine metabolism through the CYP2D6 pathway. Relationship between CYP2D6 metabolic status and clinical outcome of primaquine therapy remains to be clarified.

Drug Interactions Primaquine drug-drug interactions are likely complex and involve a multitude of pharmacological factors besides hepatic metabolism, including transporter-mediated drug-drug interactions. Primaquine has been shown to interact with ABC transporters such as P-glycoprotein (MDR1) and multidrug resistance protein 1 (MRP1). The impact that these drug-drug interactions have on primaquine efficacy is however unclear. A number of antimalarials, particularly those with a quinoline structure, i.e., mefloquine, chloroquine, quinine, and in particular primaquine itself, are all well recognized as inhibitors of hepatic CYP450 in vitro, in vivo in animals, and in man. In the chemotherapy of malaria, these antimalarials are usually co-administered either concurrently or sequentially. Metabolic drug interaction between these drugs is therefore a major concern. Results from an in vitro study showed that chloroquine, quinine, artemether, and artesunate did not significantly inhibit the formation of carboxyprimaquine by human liver microsomes. Prior treatment with chloroquine in the clinical situation had no effect on plasma primaquine pharmacokinetics in Thai patients with *P. vivax* malaria. Similarly, there appears to be no pharmacokinetic interaction between primaquine and mefloquine when used at therapeutic doses, despite mefloquine being a strong inhibitor of the formation of carboxymefloquine in vitro. Co-administration of primaquine with quinine did not alter the pharmacokinetics of primaquine but quinine. Production and/or elimination of carboxyprimaquine was reduced as indicated by the lower values of AUC within 24 h in the presence of quinine. Primaquine plasma levels and exposure have been shown to be increased when primaquine is given with chloroquine, dihydroartemisinin-piperaquine combination, and pyronaridine-artesunate combination therapy. The underlying mechanism is likely due to inhibition of CYP2D6-mediated primaquine metabolism. Some of the blood stage antimalarial agents that could interact with primaquine through CYP450 metabolic pathways also have the potential to interact with primaquine through P-glycoprotein-mediated transport.

Significant pharmacokinetic and pharmacodynamic interactions between primaquine and other drugs have been reported. The metabolic clearance of antipyrine to its three main metabolites, i.e., 3-hydroxymethylantipyrine, 4-hydroxyantipyrine, and norantipyrine, was significantly reduced after a single oral dose of 45 mg primaquine. There was no effect of primaquine on either conjugation (to paracetamol glucuronide and paracetamol sulfate) or oxidation, which supports the safety of using paracetamol as an antipyretic in malaria patients. In vitro studies have shown that primaquine conversion into carboxyprimaquine is inhibited by ketoconazole.

On the pharmacodynamics aspect, artesunate has been shown to reduce the appearance of gametocytemia in adult Thai patients infected with uncomplicated *P. falciparum* malaria, whereas its combination with primaquine resulted in shorter gametocyte clearance time. Furthermore, pentobarbitone sleeping time and zoxazolamine paralysis time were prolonged in a dose-related manner after acute administration of primaquine in the rat. Adverse hematological



Pharmacology of Antimalarial Drugs, Current Anti-malarials, Fig. 4 Chemical structures of (**a**) quinine and (**b**) 3-hydroxyquinine

reactions may also occur in the presence of myelosuppressants.

Quinine

Quinine is the chief alkaloid of the bark of the Cinchona tree *(Arbor febrifuga)* indigenous to certain regions of South America. It was first used against fever in Peru, probably around 1630. The bark was employed in 1638 to treat the wife of the Viceroy of Peru. Her miraculous cure resulted in the introduction of Cinchona into Spain in 1639 for the treatment of ague. By 1640, the drug was being employed for fever in Europe. Its use was first mentioned in European medical literature in 1643 by a Belgian. The name Cinchona is reported to be a misspelling of Chinchona, the name of the Portuguese countess who allegedly used the compound first.

For almost two centuries, the bark was employed for medicine as a powder, extract, or infusion. It was not until the 1830s that the four main active constituents of Cinchona bark were isolated: two pairs of optical isomers quinine and quinidine, together with cinchonine and cinchonidine. The Cinchona alkaloids have been used ever since, for the treatment of malaria and arrhythmic heart conditions.

Chemistry and Physical Properties

Cinchona contains a mixture of more than 20 alkaloids. The most important of these are two pairs of optical isomers quinine and quinidine and cinchonine and cinchonidine. Quinidine is a dextrorotatory diastereomer of quinine. Quinine, cinchonine, and cinchonidine are levorotary.

Quinine[6-methoxy-α-(5-vinyl-2-quinuclidinyl)-4-quinolinemethanol: Fig. 4a] contains a quinoline group attached through a secondary alcohol linkage to a quinuclidine ring. A methoxy side chain is attached to the quinoline ring and a vinyl to the quinuclidine. The molecular weights of base, sulfate, bisulfate, hydrochloride, and dihydrochloride are 324, 747, 782, 361, and 397, respectively. The salts are freely soluble in water. The drugs should be stored in air-tight containers and be protected from light.

Pharmacological Activities

Antimalarial Activity and Mechanism of Action and Resistance Quinine is a potent blood schizontocidal (large rings and trophozoites) against all species of *Plasmodium* and also gametocytocidal against *P. malariae*, *P. ovale*, *P. vivax*, and *P. knowlesi.* Quinine has no tissue schizontocidal or sporontocidal activity. The metabolites exhibit lower antimalarial potency than the parent drug.

The molecular mechanism of action of quinine against *P. falciparum* is only partially understood. Like chloroquine, quinine accumulates in the parasite digestive food vacuole and inhibits the heme detoxification process. Decreasing sensitivity to quinine has also been reported in some areas where the drug has been used extensively for malaria therapy. The genetic basis of quinine resistance involves multiple genes. Similar to chloroquine resistance in *P. falciparum*, quinine resistance is also associated with mutations of the two transport proteins, PfCRT and PfMDR1. In addition, the transport protein PfNHE1 (*Plasmodium falciparum* sodium/proton exchanger 1) encoded by the *P. falciparum* Na+/H+ exchanger gene *pfnhe* on chromosome 13 is also involved.

Other Pharmacological Activities and Clinical Uses Apart from malaria, quinine is also used to treat lupus and arthritis. The drug was previously frequently prescribed as an off-label treatment for leg cramps at night, but this

has become less common due to a Food and Drug Administration warning that this practice is associated with life-threatening adverse reactions.

Quinine has oxytocic potential to induce premature labor. It is therefore used to augment labor and also to induce abortion.

Therapeutic Indications for Malaria

Quinine and its dextroisomer quinidine are one of the most commonly used drugs for malaria treatment worldwide. Quinine is a basic amine and is usually provided as a salt. Various existing preparations include the hydrochloride, dihydrochloride, sulfate, bisulfate, and gluconate. All quinine salts can be given by oral or intravenous (IV) routes of administration. Quinine gluconate may also be given intramuscularly (IM) or rectally (PR).

Parenteral quinine (IV and IM) is indicated for the treatment of severe malaria. Parenteral quinine proved safe and effective in the treatment of severe falciparum malaria if rate-controlled intravenous infusion is used. Slow intravenous infusion of quinine dihydrochloride 10 mg/kg bw over 4 h is now the standard method of administering quinine in severe malaria. A loading dose of quinine (20 mg/kg bw quinine dihydrochloride equivalent to 16.7 mg base), infused over 4 h, has proved to be a safe method of achieving immediate therapeutic plasma concentrations for *P. falciparum*. The loading dose of quinine is however contraindicated in patients with previous treatment with quinine, quinidine, or mefloquine within 48 h. In other areas where the parasite is still sensitive to quinine, a loading dose may not be necessary. In areas with excessive use of quinine, it is too dangerous to give loading dose routinely in every patient. Severe cardiac arrhythmia has been seen in patients who were treated with quinine prior to receiving a loading dose.

In pregnancy, quinine can still be used safely and effectively in the treatment of acute uncomplicated falciparum malaria. No abortion is observed when quinine is administered to pregnant women during the first trimester. In the second and third trimester, increase in uterine contractions and fetal distress may occur during the first 24 h after the start of treatment when fever is probably still high. A 7-day quinine is strongly recommended for treatment of pregnant women in the first trimester with uncomplicated *P. vivax, P. ovale, P. malariae,* or *P. knowlesi.* In the first trimester of pregnancy and children aged lower than 8 years, quinine-clindamycin combination is used since tetracyclines are contraindicated. A 7-day oral quinine in combination with tetracycline, doxycycline, or clindamycin is used in the treatment of uncomplicated *P. falciparum* malaria as an alternative treatment when an effective ACT is not promptly available. The addition of these antibiotics improves clinical efficacy of quinine, probably through mechanisms involving both pharmacokinetic and pharmacodynamic interactions, and allows for shortening of treatment regimens. Nevertheless, patients' compliance is the major problem with all these 7-day regimens as it is difficult to achieve without hospitalization. Once the malaria symptoms have subsided, patients are reluctant to continue taking quinine because of cinchonism; poor compliance and subsequent incomplete treatment of patients who remain parasitemic are favorable to the selection of parasites less sensitive to quinine.

Adverse Reactions and Toxicity

Quinine has a narrow therapeutic window. Serious adverse reactions are infrequent, but minor adverse effects are common. In general, patients with malaria, particularly children, tolerate high blood concentrations of quinine well. Adverse reactions are less frequent than in healthy subjects due to the increased plasma protein binding of quinine in patients with malaria. Most of the adverse reactions are concentration dependent and become more frequent at high plasma concentrations. The characteristic symptom complex of cinchonism commonly occurs, which in its mild form consists of tinnitus, headache, lightheadedness, nausea, vomiting, and slight disturbance of vision. This symptom complex is transient and frequently occurs when plasma quinine levels exceeded 5 mg/l, but it disappears spontaneously after discontinuation of the drug. With the higher doses, these adverse reactions become more severe. The eighth nerve damage occurs with vertigo and decreased auditory acuity. Visual damage with blurred vision, disturbances of color

perception, night blindness, and diplopia indicate optical nerve involvement. Anorexia, vomiting, constipation, abdominal pain, and diarrhea may occur after therapeutic doses of quinine. These gastrointestinal effects are due both to the local irritant effect of quinine on the gastrointestinal tract and the central effects of quinine on the chemoreceptor trigger zone. Quinine is also a common cause of drug-induced thrombocytopenia and the most common cause of drug-induced thrombotic microangiopathy.

Quinine and its diastereoisomer quinidine including some of the metabolites (3-hydroxyquinidine, 2'-oxyquinidine, and quinidine *N*-oxide) possess cardiovascular effects. Quinidine is more likely to produce cardiac effects than quinine. The most serious reactions are associated with rapid injection of a large dose, leading to toxic blood concentrations which result in hypotension, cardiac conduction disturbances (heart block, ventricular fibrillation), or even death. When the drugs are administered by slow intravenous infusion or orally, these life-threatening adverse reactions are rare. The only effects are minor ECG changes (lengthening of the QTc interval, widening of the QRS complex, and T-wave flattening). These potentially dangerous adverse effects must be of concern particularly in patients with history of pre-existing quinine or quinidine therapy. Whenever parenteral therapy is used in severely ill patients, cardiac monitoring is recommended. Young children with severe malaria might be more susceptible to quinine cardiotoxicity than older children.

Cinchona alkaloids stimulate insulin release from pancreatic islet cells, resulting in low levels of blood glucose in malaria patients. However, malarial infection itself may also produce hypoglycemia, particularly in severe infections. During intravenous quinine therapy, potentiation of these effects can be seen more frequent in severe falciparum malaria. Pregnant women and children also appear particularly prone to quinine-induced hypoglycemia. Blood glucose levels should be monitored when the drugs are being used in pregnant patients, children, or severely ill patients.

An overestimated property of quinine is its oxytocic potential to induce premature labor. Quinine has been used to augment labor and also to induce abortion. However, the abortifacient doses of quinine are two to three times greater than those used for malaria. In addition, it has been demonstrated that malaria itself may have more oxytocic effect than quinine. Pregnancy therefore is not a contraindication to the use of quinine in the treatment of malaria.

Less frequent but more serious adverse reactions of quinine include urticaria, asthma, thrombocytopenia, bronchospasm, angioedema, and hemolysis. Interrupted and recurrent quinine therapy in nonimmune individuals with *P. falciparum* infections seems to predispose them to the complication of blackwater fever, a syndrome of severe hemolytic anemia, hemoglobinuria, oliguria, and jaundice. Occasionally, quinine and its stereoisomer quinidine have also been reported to aggravate weakness in myasthenia gravis. The use of quinine for treatment of cramp up to 60 days can be associated with rare but life-threatening adverse effects. Its used for this purpose is therefore restricted in some countries.

Quinine poisoning is uncommon but can cause serious retinal and cardiovascular toxicity.

Contraindications

Quinine is contraindicated in patients with known hypersensitivity to quinine, any of the cinchona alkaloids, or other structurally related drugs.

Caution

Although there is little evidence of cardiotoxicity in patients with malaria, quinine should be used with caution in patients who have heart rhythm disorders or heart disease. Quinine metabolites may cause oxidative hemolysis, and its use in patients with G6PD deficiency should be with caution. Plasma quinine may accumulate in patients with hepatic or renal diseases, and caution is also advised in treating these patients with quinine.

Pharmacokinetics

Pharmacokinetic parameters of quinine following currently recommended doses for treatment of uncomplicated and severe malaria are summarized in Table 1.

Quinine is rapidly absorbed following both oral and parenteral routes. C_{max} is reached 1–6 h after a single oral dose. A loading dose of 20 mg/kg bw immediately reaches 93% of C_{max} and 75% of the steady-state trough levels. Rapid intravenous injection results in high toxic concentrations which affect the cardiovascular system. Constant quinine dihydrochloride infusion of 20 mg (salt)/kg bw over 4 h as a loading dose, followed by 10 mg (salt)/kg bw intravascular infusion over 2 h, given 8 hourly for 7 days give satisfactory concentration profiles with reduced risk for cardiovascular toxicity. Intramuscular injection and oral administration produce plasma concentrations lower than those following intravenous infusion. Intramuscular quinine is slowly absorbed with t_{max} of about 5 h. A loading dose of 20 mg (salt)/kg bw provides a satisfactory plasma concentration and can be considered as alternative route of administration if the intravenous route is not possible.

Pharmacokinetics of quinine after intravenous injection is generally described by two exponential terms with a rapid distribution phase with a short half-life of about 2 min and a slower $t_{1/2}$ similarly to that after the oral dose. The Vc/F is approximately one-third of the Vd/F. Due to this pharmacokinetic property, it is therefore suggested that intravenous administration of quinine should be given by rate-controlled infusion in order to avoid potentially toxic blood concentrations early in the distribution phase.

Quinine is distributed throughout most of the body fluids and is detectable in cerebrospinal fluid (CSF), breast milk, and placenta. Approximately 85% of the drug is bound to plasma proteins, mainly to α_1-acid glycoprotein. Unlike chloroquine, and mefloquine, quinine is not concentrated in red cells. The concentration in erythrocytes is between one-fifth and one-third of that in plasma. Quinine is measurable in saliva within a few minutes of oral dosing or intravenous infusion. It remains detectable for up to 36 h after a 500 mg dose. Saliva concentrations could therefore be used as a noninvasive method to measure patients'compliance. Concentrations in saliva which represent the unbound fraction of quinine are approximately one-quarter to one-third of the plasma concentrations. Quinine concentration-time profiles for plasma, red cells, and saliva are parallel, giving similar estimation of $t_{1/2}$ in all three media. Quinine does not freely cross the blood-brain barrier. The concentrations in CSF have been reported between 2% and 7% of the corresponding plasma concentrations. The ratio of CSF/plasma free quinine concentrations is approximately 0.55.

Hepatic biotransformation accounts for about 80% of its total clearance. Quinine undergoes extensive hepatic biotransformation, predominantly via CYP3A4/5 as well as CYP2C9, CYP1A2, and CYP2D6 into several metabolites. 3-hydroxylation mainly via hepatic CYP3A4/5 to its primary metabolite, 3-hydroxyquinine (Fig. 4b), has been shown to contribute 5–10% of the antimalarial activity. Formation of the minor metabolites (10*S*)-11-dihydroxydihydroquinine and 2Ľ-quininone) is also dependent on CYP3A4/5, while the formation of (10*R*)-11-dihydroxydihydroquinine might be linked to CYP2C9. The drug and its metabolites appear in the urine within 1 h of drug administration, and little remains in the body after 48 h. Elimination from the body is rapid with CL/F of about 0.2–5 ml/min/kg. About 20% of quinine is excreted unchanged in the urine, and small amounts may appear in the bile and saliva. Renal excretion involves by both glomerular filtration and tubular secretion. There appears to be stereoselective net renal tubular secretion of quinidine over quinine which indicates stereoselectivity of the renal tubular transport process.

Factors Associated with Altered Drug Exposure and/or Treatment Response

Malaria Infection The pharmacokinetics of quinine is significantly altered by malaria infection. The absorption is not affected, but the CL/F is reduced from 0.2 to 5 ml/min/kg in healthy subjects to about 1.4 and 0.9 ml/min/kg in uncomplicated malaria and cerebral malaria, respectively. The excretion of quinine is inversely related to disease severity and most impeded in severe malaria infection. It is likely that the main factor that influences the decreased clearance of quinine is the impairment of CYP3A4/5 function. The Vd

is contracted (1.1 l/kg) in cerebral malaria. The $t_{1/2}$ is prolonged during acute infection with a mean of 16 h or even longer in severe malaria (18 h). Consequently, elevation of plasma drug concentrations is observed which is also proportional to the severity of the disease. Despite such high plasma concentrations in severe falciparum malaria, there is no apparent quinine toxicity. This is explained by the increase in plasma protein binding of quinine to α_1-acid glycoprotein in patients with cerebral malaria (93%). The extent of increase in plasma protein binding of quinine is relatively lower in uncomplicated malaria (90%). Despite the marked reduction of quinine clearance in severe malaria, maintenance dose reduction is not recommended in the initial phase of treatment because severe infections cause high early fatality rates. The danger of inadequate treatment overweighs the risk of toxicity. The dose should be reduced in severe malaria only when there is evidence of severe cardiotoxicity or persistent renal failure after 3 days of treatment (by this time enough quinine is available for consistent parasiticidal activity). Dose reduction by one-third after 3 days has been suggested to prevent further rise in plasma quinine concentrations in such cases. In the presence of severe arrhythmia, discontinuation of quinine treatment should be considered if effective alternative drugs such as artemisinin drugs are available.

Children The disposition of quinine changes with age with slightly higher concentrations observed in children aged lower than 2 years. In children with malaria, the Vd is contracted (30% smaller) and the CL is increased. As a result of these changes, shorter $t_{1/2}$ is observed in children. The decline in plasma concentrations of quinine in the latter half of the treatment course (10 mg base/kg bw every 8 h for 7 days) is associated with treatment failure when values fall below the putative minimum inhibitory concentration (MIC). For this reason it has been suggested that the individual dose of quinine in children should be increased to 15 mg base/kg body weight in the second half of the treatment course.

Elderly Subjects Disposition kinetics of quinine is altered in healthy elderly subjects when compared to those of younger adult subjects. The rate of drug absorption is not altered, but the CL/F is significantly reduced (26% reduction). The lower CL/F in the elderly group indicates the decreased hepatic biotransformation of quinine in old age, since the renal clearance of drug is not altered. This results in a prolongation of the $t_{1/2}$ (about 18.4 h). Plasma protein binding of quinine remains unchanged despite the lower plasma albumin. This is due to the fact that quinine binds extensively to α_1-acid glycoprotein rather than albumin. Significant drug accumulation may occur after multiple dosing of malaria treatment. The clinical significance of this finding is unclear, but it emphasizes the need for caution in the administration of quinine to elderly patients.

Malnutrition Intestinal malabsorption is a feature of kwashiorkor. This condition significantly affects the pharmacokinetics of quinine. The longer apparent absorption half-life ($t_{1/2a}$) and t_{max} and the lower C_{max} observed in patients with kwashiorkor suggest slower and lower absorption of quinine in this group of patients, although the contribution from differences in distribution kinetics cannot be excluded. Quinine is eliminated more slowly in children with kwashiorkor, and therefore, $t_{1/2}$ is significantly prolonged. Enlarged fatty liver is common in kwashiorkor, and this is associated with reduced activity of some of the oxidative liver enzymes.

Pregnancy Quinine is one of the first-line drugs recommended for use during the first trimester of pregnancy. The pharmacokinetic properties of quinine are not different between pregnant and nonpregnant women with uncomplicated malaria. In severe malaria, the Vd/F is generally reduced by about 30%, and elimination is more rapid. Alterations in plasma protein and tissue protein binding associated with malaria infection and pregnancy itself may be responsible for the reduction in the Vd. Placental cord plasma quinine concentrations range between 1 and 4.6 mg/l, which correlate well with maternal plasma quinine concentrations. The mean ratio of cord

plasma to maternal plasma quinine concentration is 0.32 and considered safe for breast-feeding. Breast milk-to-plasma ratio ranges from 0.11 to 0.53.

Hepatic Diseases Hepatic metabolism of quinine is reduced in hepatic insufficiency. Pharmacokinetics of quinine during the acute phase of hepatitis-B infection is significantly different from those in healthy subjects. The $t_{1/2}$ is prolonged (17 h) and CL/F is reduced. However, the pharmacokinetics obtained during acute hepatitis is not different from those during the recovery phase. Despite a return of liver function tests to normal during convalescence after hepatitis, the clearance of quinine remains impaired. This suggests that curative regimens of quinine used in the routine treatment of falciparum malaria may not be suitable for malaria patients with acute hepatitis or even those who have had hepatitis within the past 3 months. The combined effects of acute hepatitis and malaria on the kinetics of quinine suggest caution with its dosage in patients with both conditions.

Renal Diseases Quinine clearance is reduced in acute renal failure complicating malaria, but this is the result of pharmacokinetic changes related to the acute infection rather than due to reduced renal function per se*,* as urinary quinine clearance comprises only 20% of the total clearance. Hemofiltration has no significant influence on the total body clearance of quinine.

Genetic Polymorphisms of Drug-Metabolizing Enzymes Substantial variation of quinine pharmacokinetics between individuals was observed in children from Ghana with severe malaria. The possible involvement of polymorphisms of drug-metabolizing enzymes has been proposed but remains to be confirmed. One study showed that 3-hydroxylation metabolite of quinine is substantially lower in healthy people from Tanzania harboring the *CYP3A5*3/*3* low-expression genotype.

Drug Interactions Various studies suggest significant pharmacodynamic and pharmacokinetic interactions between quinine and other drugs including other antimalarial drugs. The QTc interval may be prolonged when quinine is given with antiarrhythmic drugs such as flecainide and amiodarone. In addition, ventricular arrhythmia may occur when the drug is given with antihistamines (e.g., terfenadine) or antipsychotic drugs (e.g.*,* thioridazine). Quinine has been shown to potentiate the oral anticoagulants by inhibition of prothrombin synthesis.

With regard to pharmacokinetic interactions, systemic exposure of quinine is unchanged when quinine is co-administered with sulfadoxine-pyrimethamine (SP) and oral contraceptive steroids. On the other hand, plasma quinine concentrations are increased when co-administered with tetracycline, quinidine/cinchonine, cimetidine, ketoconazole, omeprazole, nifedipine, troleandomycin, and erythromycin. The mechanism involved is mainly through hepatic CYP450 inhibition. Plasma quinine concentrations in the presence of tetracycline are significantly higher than those with quinine alone. The addition of the course of tetracycline (250 mg, 6 hourly for 7 days) to the conventional regimen of quinine (600 mg 8 hourly for 7 days) has an influence on the maintenance of plasma quinine concentrations above the MIC throughout the 7-day period of treatment. Higher plasma concentrations of each component have also been observed when quinine, quinidine, and cinchonine were given in combination.

Drugs which have been shown to reduce systemic exposure of quinine include rifampicin, isoniazid, lopinavir/ritonavir (LPVr), and activated charcoal. Acidification of the urine also increases the excretion rate of quinine by about twofold resulting in low systemic exposure. Rifampicin and isoniazid decrease plasma quinine concentrations, possibly by the induction of hepatic metabolism of quinine. Following 1 week pre-treatment with rifampicin and isoniazid, the CL/F of quinine is significantly increased, and the $t_{1/2}$ is shortened. The combined therapy of quinine and rifampicin for *P. falciparum*, however, resulted in faster parasite clearance which could be due to antimalarial

activity of rifampicin rather than drug interaction, since induction of CYP3A4-mediated quinine metabolism activity by rifampicin takes several days. Quinine penetrates relatively poorly into the cerebrospinal fluid (CSF) in patients with cerebral malaria, with a concentration of approximately 2–7% of plasma concentrations. Co-administration of rifampicin and quinine may also decrease quinine concentrations in the CSF due to inducing effect of rifampicin on the efflux protein P-glycoprotein. Rifampicin should, therefore, not be combined to antimalarial for malaria treatment despite its intrinsic antimalarial activity.

Concomitant use of antimalarial and antiretroviral drugs is increasingly frequent in malaria and HIV-endemic regions. The reduction in systemic exposure of quinine and 3-hydroxyquinine with concomitant LPV/r use (ritonavir-boosted lopinavir) raises concerns of suboptimal exposure. The rate of elimination of a therapeutic dose of quinine is increased when activated charcoal is administered at regular intervals commencing 4 h after therapeutic dose of quinine (600 mg). Activated charcoal shortens quinine $t_{1/2}$ and increases CL by approximately 50%. Recently, it has been shown that repeated oral charcoal (50 g, 4 hourly) is highly effective and is only one approach in enhancing the removal of quinine in symptomatic patients with acute quinine poisoning to reduce the risk of potentially dangerous complications.

Quinine inhibits the activity of CYP2D6 as well as P-glycoprotein and biliary excretion. It has been shown to interact with antipyrine, digoxin, ampicillin-cloxacillin, and rifampicin upon co-administration. Quinine inhibits biliary excretion and may theoretically alter rifampicin $t_{1/2}$. Chronic administration of quinine shortens plasma antipyrine $t_{1/2}$. Quinine increases digoxin plasma levels, probably by reducing its nonrenal clearance. Quinine reduced the bioavailability and the antimicrobial activity of ampicillin-cloxacillin upon co-administration, which may have therapeutic implications. The MIC of both antibiotics in the presence of quinine was five- to sevenfold increased, indicating a decrease in antimicrobial activity by quinine.

Mefloquine

During the Second World War, the US Army initiated a program for the discovery and development of new antimalarial drugs. The most promising chemical class to emerge from this extensive research program was found to exhibit phototoxic adverse effects, and thus its further development was precluded. In 1960, following the emergence of chloroquine-resistant *P. falciparum* in Southeast Asia, the search continued, and the compound selected from this class was WR 142490. It was proved both to be safe and reliably effective. This compound was later named mefloquine. Since then, the development of mefloquine was continued by the World Health Organization (WHO) in collaboration with Hoffmann-La Roche and the US Walter Reed Institute of Research (WRIR). The initial phase I and II clinical trials were carried out between 1972 and 1978 in many tropical countries including Zambia, Brazil, Vietnam, and Thailand. Results showed mefloquine to be safe, generally well tolerated, and therapeutically effective in a single dose of 750–1500 mg against both chloroquine-resistant and chloroquine-sensitive *P. falciparum*, with initial cure rates approaching 100%.

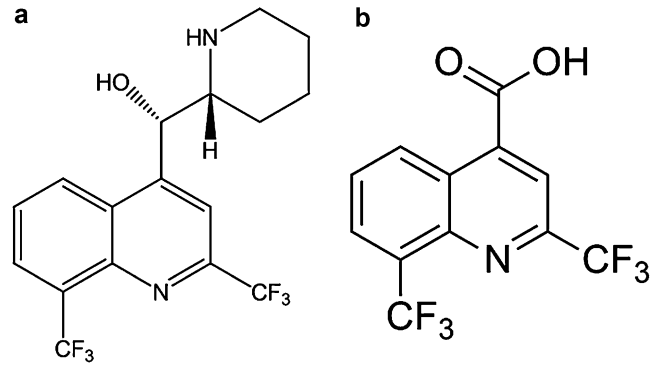
Chemistry and Physical Properties

Mefloquine (Fig. 5a) is a 4-quinolinemethanol derivative which has two asymmetric carbon atoms in the molecule and is used clinically as a racemic mixture (50:50) of the erythro isomers (dextrorotatory 11R, 2'S and levorotatory 11S, 2'R).

Mefloquine is poorly soluble in water (10 g/l at 6°C). The molecular weight of the base is 378. The hydrochloride salt (MW 415) is a white, odorless, and bitter tasting powder. It is slightly soluble in water. The drug has a tendency to bind to cell membranes, proteins, and plastics.

Pharmacological Activities

Antimalarial Activity and Mechanism of Action and Resistance Mefloquine is a potent and long-acting blood schizontocidal antimalarial against all human species of *Plasmodium* including multidrug-resistant strains of *P. falciparum*. In



Pharmacology of Antimalarial Drugs, Current Anti-malarials, Fig. 5 Chemical structures of (**a**) mefloquine and (**b**) carboxymefloquine

addition, it is active against gametocytes of *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi.* However, it has no effect against exoerythrocytic forms of malaria. Its major plasma metabolite carboxymefloquine (Fig. 5b) has no significant antimalarial activity. Mefloquine exhibits approximately the same stage specificity of action as quinine, killing primarily the large rings and trophozoites of asexual parasites.

The exact modes of antimalarial action and resistance of mefloquine remains unclear. It is thought that mefloquine may share some mechanisms with chloroquine and quinine. Three possible mechanisms of action of mefloquine have been proposed: the impairment of NADPH oxidation process through its interaction with phospholipids in the parasite membrane, the interaction with ferriprotoporphyrin IX (FPIX), and the action on the parasite food vacuoles, raising intravesicular pH and thereby interfering with food digestion of the parasites. A more recent proposal is inhibition of endocytosis of the cytosol by the parasite.

Mefloquine was first introduced as first-line treatment for *P. falciparum* malaria in Thailand in 1984. However, despite its restricted clinical uses, significant resistance developed within 6 years. Resistance is now spread to several malaria-endemic areas particularly Southeast Asian countries. Resistance of *P. falciparum* to mefloquine is shown to be mediated by amplification of *pfmdr1*, leading to overexpression of the encoded digestive membrane transporter PfMDR1. Studies on transgenic parasites later on demonstrate that reduced parasite susceptibility to mefloquine is associated with increased pfMDR1-mediated import into parasite food vacuole. This suggests that a primary target (s) of action of mefloquine resides outside digestive food vacuole. Inhibition of the import of many compounds into the food vacuole by mefloquine has been shown.

Other Pharmacological Activities and Clinical Uses Mefloquine exerts in vitro and in vivo activity against *Mycobacterium avium* complex including strains with multidrug resistance. In addition, it is also found to be effective against *Schistosomes.* A single dose of mefloquine possesses potential effect against three major species of schistosomes (*Schistosoma mansoni*, *Schistosoma haematobium*, and *Schistosoma japonicum*) infecting humans. When used as IPTp for malaria prevention, mefloquine shows promising activity against concomitant *S. haematobium* leading to reduction of egg excretion in pregnant women.

Therapeutic Indications for Malaria

Mefloquine is currently recommended by WHO for the chemoprophylaxis of malaria caused by all *Plasmodium* species. In addition, it is also recommended for treatment of uncomplicated malaria in combination with artesunate (one of the ACTs). As there is no parenteral form of mefloquine, the drug is generally not used in severe malaria. In addition, mefloquine is contraindicated in cerebral malaria due to CNS toxicity.

For prophylaxis, mefloquine is likely to be an effective chemoprophylactic agent for long-term use (4–6 weeks). Its use is recommended for 6 months and beyond with clinical controls. It is the only prophylactic drug recommended for first-trimester pregnancies and considered safe throughout pregnancy. The dose of 250 mg base (274 mg mefloquine hydrochloride) weekly has been recommended, but the maintenance of this dose level beyond 12 weeks may entail accumulation and increase incidence of adverse reactions.

For treatment of uncomplicated malaria, a total therapeutic dose of 4 (2–10) mg/kg bw *per* day artesunate and 8.3 (5–11) mg/kg bw *per* day mefloquine, given once a day for 3 days, is recommended. Formulations are currently available as fixed-dose artesunate-mefloquine combination as pediatric tablets containing 25 mg artesunate and 55 mg mefloquine hydrochloride (50 mg base) and adult tablets containing 100 mg artesunate and 220 mg mefloquine hydrochloride (200 mg base). To reduce vomiting, mefloquine dose should be split over 3 days as in current fixed-dose combination.

Adverse Reactions and Toxicity

Mefloquine is generally well tolerated when given alone or in combination with artesunate. The majority of adverse reactions after therapeutic or prophylactic dose of mefloquine are mild, transient, and require no specific treatment. Severe adverse reactions are rare. Adverse reactions appear to be associated with high concentrations of the (−) enantiomer rather than the racemic mefloquine and are more frequent in females than males.

Nausea, vomiting, abdominal pain, and diarrhea are the most common adverse effects after mefloquine in patients with malaria. Nausea and vomiting are dose related, being more likely in adult patients receiving higher dosage than 15 mg/kg bw. Vomiting is rarely observed in healthy subjects after drug administration. Onset of nausea and vomiting from mefloquine is rapid (within the first few hours after drug administration); it is therefore suspected to be the result of a local effect (i.e., gastric irritation) rather than a central effect of mefloquine. In addition, nausea is unlikely to be a function of mefloquine blood concentrations as there is evidence that the incidence of this symptom is decreased when an antiemetic, metoclopramide, is given prior to mefloquine administration, despite an increase in C_{max} and systemic exposure of mefloquine. Vomiting within the first hour after drug administration has been shown to result in low plasma concentrations which lead to treatment failure. Diarrhea after mefloquine is usually mild in the majority of cases, occurring in 10–50% of patients who are treated with mefloquine, with an average duration of 2–3 days.

Mefloquine has been associated with seizures, anxiety, irritability, dizziness, paranoia, suicidal ideation, depression, hallucinations, and violence during therapeutic dose regimen and long-term malaria prophylaxis. Such neuropsychiatric reactions generally resolve after discontinuation of the drug. The estimated incidence of seizures, encephalopathy, or psychotic reactions ranges from 1 in 10,000 healthy people receiving chemoprophylaxis, 1 in 1000 malaria patients in Asia, 1 in 200 malaria patients in Africa, to 1 in 20 patients recovering from cerebral malaria.

Less frequently reported adverse reactions include effects on blood and lymphatic (agranulocytosis, aplastic anemia), nervous (syncope, convulsions, abnormal coordination, memory impairment, sensory and motor neuropathies including paresthesia, tremor and ataxia, and encephalopathy), cardiovascular (tachycardia, palpitation, QTc prolongation, bradycardia, irregular heart rate, extrasystoles, A-V block, and other transient cardiac conduction alterations), eye and ear (visual disturbances, tinnitus, and hearing impairment), gastrointestinal (dyspepsia), and immune (hypersensitivity reactions ranging from mild cutaneous events to anaphylaxis) systems. Hypersensitivity reactions including anaphylaxis and pneumonitis have also been associated with the use of mefloquine. As with most medications, hypersensitivity reactions, ranging from mild cutaneous events to anaphylaxis, cannot be predicted.

Rare reactions include edema, chest pain, asthenia, malaise, fatigue, chills, pyrexia, anorexia, muscle weakness, muscle cramps, myalgia, arthralgia, drug-related hepatic disorders

(from asymptomatic transient transaminase elevations to hepatic failure), and blood disorders (decreased hematocrit, transient elevation of transaminases, leukopenia or leukocytosis, and thrombocytopenia). There has been no evidence of hemolytic effect of mefloquine in subjects with G6PD deficiency.

Mefloquine is not mutagenic or carcinogenic. However, it is teratogenic and embryotoxic in experimental animal. However, data from published studies in pregnant women have shown no increase in the risk of teratogenic effects or adverse pregnancy outcomes following mefloquine treatment or prophylaxis during pregnancy. Prophylactic doses of mefloquine in the second or third trimesters of pregnancy appear to be effective and are not associated with adverse maternal or fetal outcomes. However, gastrointestinal adverse reactions including nausea and vomiting are common in pregnant women treated with mefloquine.

Contraindications

Mefloquine is contraindicated in patients with a known hypersensitivity to mefloquine or structurally related compounds, (e.g., quinine, quinidine, chloroquine, or amodiaquine). The drug should not be prescribed for follow-up treatment after cerebral malaria. Mefloquine prophylaxis is contraindicated in patients with active depression or a history of psychiatric disturbances (including depression, generalized anxiety disorder, psychosis, schizophrenia, or other major psychiatric disorders) or a history of convulsions, since the drug may precipitate these conditions.

Caution

Patients with hepatic impairment who receive mefloquine should be monitored carefully for the potential of the increased risk of adverse reactions. Caution should also be made in administering mefloquine to patients with cardiac disease or in concurrent with drugs that alter cardiac conduction (e.g., antiarrhythmics, β-adrenergic blocking agents, calcium channel blockers, antihistamines (astemizole, terfenadine), tricyclic antidepressants, phenothiazines, and the antimalarial drugs quinine, halofantrine, and mefloquine). As small amount of mefloquine is excreted in breast milk, the use of mefloquine in nursing women should be with caution.

Pharmacokinetics

Pharmacokinetic parameters of mefloquine following currently recommended doses for prophylaxis and treatment of uncomplicated malaria are summarized in Table 1.

Oral absorption of mefloquine is relatively slow. The absolute oral bioavailability of mefloquine cannot be determined since an intravenous formulation is not available. The bioavailability of the tablet formulation compared with an oral solution is over 85%. When taking mefloquine with food, the extent and rate of absorption of mefloquine are increased leading to about a 40% increase in bioavailability, increased in C_{max}, and shortened t_{max}. Plasma concentrations peak 8–15 h after a single oral dose of mefloquine. There is considerable enterohepatic circulation impacting on t_{max} and C_{max} leading to high variability of plasma/blood concentrations. At the prophylactic dose of 250 mg once weekly, maximum steady-state plasma concentrations of 1000–2000 ng/ml are reached after 7–10 weeks.

Mefloquine is extensively bound to plasma proteins and also to tissue and red cell membranes. Plasma protein binding is 98%, mainly to α_1-acid glycoprotein. The Vd/F is relatively large, indicating extensive tissue distribution. Mefloquine may accumulate in parasitized erythrocytes at an erythrocyte-to-plasma concentration ratio of about 2. Mefloquine also crosses the placenta.

The biotransformation of mefloquine occurs in the liver by CYP3A4 into two inactive metabolites, carboxymefloquine (2-8-*bis*-trifluoromethyl-4-quinoline carboxylic acid: Fig. 5b) and hydroxymefloquine. The main metabolite carboxymefloquine is inactive against *P. falciparum*. This metabolite appears in plasma 2–4 h after a single oral dose of mefloquine. Its concentrations rise steadily and exceed those of the patent drug after in about 2–3 days. C_{max} of carboxymefloquine in plasma, approximately three to five times higher than that of mefloquine, is reached after 2 weeks. Carboxymefloquine is eliminated from plasma at a rate that is similar to that of mefloquine. The

relatively high plasma concentration of carboxymefloquine is explained by its small Vd/F. It is unlikely that much of carboxymefloquine penetrates the CNS, as it is not detectable in the CSF.

Mefloquine has been shown to be a substrate and/or inhibitor of the transporters P-glycoprotein (MDR1), multidrug resistance protein (MRP), as well as breast cancer receptor protein (BCRP). This is important because MRP1 and MRP4 (and MRP5 and BCRP) in red blood cells might affect red cell mefloquine concentrations and drug effectiveness as well as the development of drug resistance to mefloquine. By contrast, MDR1 might be more important in establishing mefloquine safety as it controls mefloquine concentrations and entry of the drug into the brain.

The $t_{1/2}$ of mefloquine varies between 2 and 4 weeks with an average of about 3 weeks. The value remains unchanged during long-term prophylaxis. Mefloquine is excreted into bile and feces. Urinary excretion of unchanged mefloquine and carboxymefloquine accounts for about 9% and 4% of the dose, respectively. Concentrations of other metabolites could not be measured in the urine. Low concentrations (3–4%) of mefloquine are excreted in breast milk following a dose equivalent to 250 mg of the free base.

The multiple-dose kinetics of mefloquine is similar to single-dose pharmacokinetics. This suggests that there is no auto-induction or auto-inhibition of the metabolic clearance mechanisms of mefloquine. The pharmacokinetics of mefloquine is also highly stereospecific. Following the administration of a single oral dose of 1000 mg mefloquine to a healthy male Caucasian, plasma and whole blood concentrations of R(−) mefloquine were greater than those of the S(+) enantiomer. The ratios of R(−) and S(+) mefloquine in plasma and whole blood ranged from 1.7 at 2 h to 11.5 at 504 h and from 1.5 at 2 h to 3 at 504 h, respectively.

Factors Associated with Altered Drug Exposure and/or Treatment Response

Malaria Infection Pharmacokinetics of mefloquine appears to be altered in malaria. Absorption of the drug is usually not changed in uncomplicated falciparum malaria. In severely ill patients, i.e., cerebral malaria, absorption may be incomplete despite the apparent rapidity in the rate of absorption. The Vd/F is contracted and CL/F is reduced during an acute phase of malaria infection. However the effect on clearance is less predictable as the elimination rate is increased in patients with malaria. Indirect evidence from a few studies suggests that the shorter $t_{1/2}$ of mefloquine in patients with uncomplicated falciparum malaria may be caused by an interruption of enterohepatic recycling (EHC) of mefloquine in malaria. The pharmacokinetic alterations resulting from the interruption of EHC by broad-spectrum antibiotics ampicillin and tetracycline closely resemble those observed in patients with uncomplicated malaria.

Ethnics Pharmacokinetic variability of mefloquine has been observed among various ethnic populations. Mefloquine concentration in healthy Thai subjects is higher than that in Caucasian subjects, while comparable pharmacokinetics is reported among Brazilian, Caucasian, and African subjects. In practice, however, these are of minor importance with regard to drug efficacy.

Children No relevant age-related changes have been observed in the pharmacokinetics of mefloquine. Clinical experience has not identified differences in responses between the elderly and younger patients. Children with uncomplicated falciparum malaria showed a good absorption with blood concentrations comparable to those seen in adults.

Pregnancy Although the rate of mefloquine absorption in late pregnancy is unchanged, C_{max} and systemic availability are significantly reduced during the first 2 days of mefloquine administration. The oral bioavailability of mefloquine in late pregnancy may be altered as a result of delayed gastric emptying, decreased motility of the gastrointestinal tract, or changes in plasma/tissue protein binding. The expansion of the Vd/F or the increase in CL/Fcould be due to an increase in the glomerular filtration rate. Suboptimal dosing

could partially explain the poorer treatment responses observed among pregnant women.

Genetic Polymorphisms in Drug Transporters A prospective clinical trial in Caucasian travelers taking mefloquine prophylaxis.

revealed the link between polymorphisms of the P-gp (MDR1) efflux protein in the brain and incidence of neuropsychiatric adverse reactions of mefloquine. Individuals with genetic defect in the *mdr1* gene (*ABCB11236TT/2677TT/3435TT* haplotype) were associated with a particularly high risk of neuropsychiatric reactions, which were not related to mefloquine serum concentrations. A lower expression of MDR1 in individuals carrying *ABCB1 T* variants resulted in lower mefloquine efflux from the brain, exposing individuals to high tissue concentrations related to neuropsychiatric symptoms. This finding might suggest the important role of local MDR1 expression at the blood-brain barrier which leads to the accumulation of mefloquine in the brain without affecting systemic exposure. This genetic polymorphism might also affect stereoselectivity of MDR1 and consequently cerebral or plasma mefloquine (R)/(S) ratio without changing total plasma concentrations. As mefloquine is also a potent MDR1 inhibitor, propensity of drug interaction may occur when mefloquine is used concurrently with other drugs that are substrates or inhibitors of MDR1 (e.g., HIV protease inhibitors, MDR1 substrates).

Renal Diseases No pharmacokinetic study has been performed in patients with renal insufficiency since only small proportion of the drug is eliminated renally. Mefloquine and carboxymefloquine are not significantly removed by hemodialysis.

Hepatic Diseases The pharmacokinetics of mefloquine in patients with compromised hepatic function has not been investigated. Mefloquine is extensively metabolized in the liver by the CYP450 system, and it is possible that the elimination of mefloquine may be prolonged in patients with impaired hepatic function, leading to higher plasma levels.

Drug Interactions The use of drug combinations has shown to delay in emergence of mefloquine resistance in vivo in animals and in vitro when used with sulfadoxine-pyrimethamine (MSP) and with primaquine. Combination of artemisinin with mefloquine has been shown to produce potentiation in vitro, in vivo in mice infected with resistant strains, and in humans presenting with complicated falciparum malaria. The combination of mefloquine with chloroquine or desethylchloroquine exhibited pronounced antagonistic effect in vitro with both chloroquine-sensitive and chloroquine-resistant *P. falciparum.* Clinically significant QTc interval prolongation has not been reported with mefloquine alone. However, concomitant administration of mefloquine, quinine, quinidine, chloroquine, or halofantrine may produce electrocardiographic abnormalities. Inhibition of KvLQT1/minK in the human heart by mefloquine may in part explain the synergistic prolongation of QTc interval observed. Caution should also be made with other drugs that alter cardiac conduction (see also the section "Caution") since they may contribute to a prolongation of the QTc interval. Concomitant administration of mefloquine with drugs known to lower the epileptogenic threshold (antidepressants, bupropion, antipsychotics, tramadol, quinine, quinidine, or chloroquine) may increase the risk of convulsions.

When mefloquine is taken concurrently with oral live typhoid vaccines, attenuation of immunization cannot be excluded. Vaccinations with attenuated live bacteria should therefore be completed at least 3 days before the first dose of mefloquine.

Blood (plasma or whole blood) concentrations of mefloquine have been shown to be increased when co-administered with metoclopramide, ketoconazole, quinine, ampicillin, and tetracycline. The risk of QTc prolongation and other adverse reactions of mefloquine may also be expected if these drugs are taken during mefloquine therapy for prophylaxis or treatment of malaria. The antiemetic metoclopramide, through stimulation of gastric emptying rate, increases the absorption of mefloquine, resulting in higher C_{max} and AUC in the first 24 h of treatment. Metoclopramide would seem to have an important role in prevention of vomiting before antimalarial administration in

malaria patients. Co-administration of ketoconazole, a strong inhibitor of CYP3A4, increases plasma concentrations of mefloquine (AUC by 79% and C_{max} by 64%) and prolongs $t_{1/2}$ (by 39%). Mefloquine concentration has been reported to rise abruptly after the cessation of quinine administration. Competition for plasma and red cell binding site(s) of mefloquine might explain this interaction. Cardiotoxicity is therefore a major concern as there is a report of the sudden death of a patient who concurrently administered mefloquine and quinine.

In the chemotherapy of malaria, tetracycline has an important role in the treatment of falciparum malaria when given in combination with other blood schizonticides. When tetracycline is given in combination with quinine, chloroquine or sulfadoxine-pyrimethamine, and mefloquine, the cure rate is improved. Pharmacokinetic interaction studies demonstrated that the $t_{1/2}$, mean residence time (MRT) and apparent volume of distribution at steady state (Vd_{ss}/F) of mefloquine are all reduced when co-administered with tetracycline. In addition, C_{max} and AUC are increased during the course of tetracycline administration. Competition between these drugs for biliary excretion could conceivably occur.

Systemic exposure of mefloquine has been shown to be significantly decreased in the presence of rifampicin. Rifampicin induces mefloquine metabolism, decreasing its AUC by 68% and $t_{1/2}$ by 63%. The AUC and CL/F of carboxymefloquine metabolite are increased by 30% and 25%, respectively. Simultaneous administration of mefloquine and rifampicin should therefore be avoided.

The concomitant administration of the antimalarials primaquine, sulfadoxine-pyrimethamine as well as oral contraceptive steroids, and antipyrine does not alter the pharmacokinetics or adverse reaction profile of mefloquine. Pharmacokinetics of oral dihydroartemisinin and mefloquine when given concurrently are similar, except for the absorption rate of mefloquine which is faster in the presence of dihydroartemisinin. The pharmacokinetics of artemether, dihydroartemisinin, lumefantrine, and mefloquine are also unchanged when mefloquine is co-administered with artemether or artemether-lumefantrine combination.

Mefloquine has been reported to interact with other drugs when given concurrently. Mefloquine reduces plasma concentration of the anti-HIV ritonavir. Concomitant administration of mefloquine and anticonvulsants may reduce seizure control by lowering the plasma levels of the anticonvulsants. Therefore, patients concurrently taking anticonvulsant medication, including valproic acid, carbamazepine, phenobarbital, phenytoin, and mefloquine, should have the blood level of their anticonvulsants monitored and the dosage adjusted appropriately.

A single case in the literature reports a transient severe psychiatric disturbance, suggesting an adverse reaction to mefloquine associated with a heavy ingestion of alcohol (600 ml of whisky).

Carboxymefloquine has been shown to induce drug-metabolizing enzyme and transporter expression by activation of pregnane X receptor in vitro. Thus, the clinical use of mefloquine may result in pharmacokinetic drug-drug interactions via its metabolite carboxymefloquine. Whether these in vitro findings are of clinical relevance has to be addressed in future clinical drug-drug interaction studies.

Antifolates

Antifolate drugs include various combinations of dihydrofolate reductase (DHFR) enzyme inhibitors, such as pyrimethamine, proguanil, chlorproguanil, and cycloguanil, and dihydropteroate synthase (DHPS) enzyme inhibitors, such as sulfadoxine, sulfalene, and dapsone. Currently, only the sulfadoxine-pyrimethamine antifolate combination and the combination of antifolate proguanil and atovaquone are recommended for malaria treatment and/or prophylaxis.

Sulfadoxine-Pyrimethamine

Chemistry and Physical Properties

Sulfadoxine (4-Amino-N-{5,6-bis[(~2~H_3_)methyloxy]pyrimidin-4-yl}benzene-1-sulfonamide: Fig. 6a) appears as white or creamy white, almost odorless crystalline powder. The molecular weight is 310.3. It is not dissolved well in water.

Pyrimethamine (2,4-Diamino-5-(4-chlorophenyl)-6-ethylpyrimidine: Fig. 6b) also appears as white, almost odorless crystalline powder. The molecular weight is 248.7.

Pharmacology

Antimalarial Activities and Mechanisms of Action and Resistance Sulfadoxine is a sulfonamide antibacterial which acts by inhibiting the activity of dihydropteroate synthase (DHPS) and, therefore, synthesis of folic acid by bacteria and malaria parasite. On the other hand, pyrimethamine inhibits dihydrofolate reductase (DHF) and thereby the synthesis of folic acid by bacteria and malaria parasite. Both are active mainly against the later development stages of asexual *Plasmodium* parasite.

Other Pharmacological Properties The combination of sulfadoxine and pyrimethamine is used in the treatment of toxoplasmosis.

Therapeutic Indications for Malaria

Sulfadoxine-pyrimethamine is indicated in areas of moderate-to-high malaria transmission intensity for intermittent preventive treatment (IPT) of malaria in pregnant women and in infants. It is also used in combination with amodiaquine for seasonal malaria chemoprevention in children in areas with highly seasonal malaria transmission and in the few areas in which it remains effective. Sulfadoxine-pyrimethamine can be used with artesunate for the treatment of acute uncomplicated malaria in areas where the parasites are still sensitive to sulfadoxine-pyrimethamine.

In malaria-endemic areas in Africa, intermittent preventive treatment with sulfadoxine-pyrimethamine combination is strongly recommended in all women (SP-IPTp) as part of antenatal care. At least three doses of sulfadoxine-pyrimethamine are administered during pregnancy, a single oral dose of three tablets each (one tablet contains 25 mg sulfadoxine and 500 mg pyrimethamine). Dosing should start in the second trimester, and doses should be given at least 1 month apart, with the objective of ensuing that at least three doses are received.

In areas of moderate-to-high malaria transmission of Africa where sulfadoxine-pyrimethamine is still effective (no pfdhps540 mutation), intermittent preventive treatment with this combination (one to two tablets) is recommended to infants (aged lower than 12 months) (SP-IPTi) at the time of the second and third rounds of vaccination against diphtheria, tetanus, and pertussis (DTP) as well as vaccination against measles.

In areas with high malaria transmission in the sub-Sahel region of Africa, seasonal malaria chemoprevention (SMC) with monthly amodiaquine-sulfadoxine-pyrimethamine (ACT) combination is strongly recommended for all children aged lower than 6 years during each transmission season.

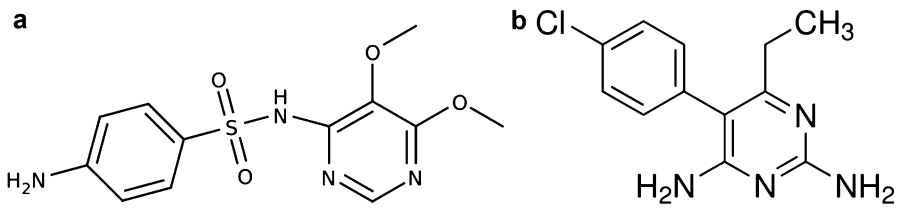
From an operational perspective, it is noted that drugs used in IPTp, SMC, and IPTi should not be used as a component of first-line treatments in the same country or region.

Adverse Reactions and Toxicity

Sulfadoxine-pyrimethamine combination is generally well tolerated at the recommended doses. Most adverse reactions are those associated with sulfonamides. These include gastrointestinal disturbances (nausea, vomiting, abdominal pain, and diarrhea), headache, dizziness, skin reactions (photosensitivity, rash, pruritus, and urticaria), and slight hair loss. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis may also occur at rare frequency. Leucopenia, thrombocytopenia, megaloblastic anemia, hemolytic anemia (probably related to G6PD deficiency), crystalluria, hematuria, oliguria, hepatitis, serum sickness, allergic pericarditis, and pulmonary infiltrates resembling eosinophilic or allergic alveolitis have also been reported.

Contraindications

Sulfadoxine-pyrimethamine alone or combination therapy with amodiaquine or artesunate is contraindicated in the following conditions: known hypersensitivity to pyrimethamine, sulfonamides, and structurally related compounds; megaloblastic anemia due to folate deficiency; premature or newborn infants in the first 2 months of life;



Pharmacology of Antimalarial Drugs, Current Anti-malarials, Fig. 6 Chemical structures of (**a**) sulfadoxine and (**b**) pyrimethamine

HIV-infected patients receiving cotrimoxazole prophylaxis against opportunistic infections; and pregnancy in the first trimester.

Caution

The use of sulfadoxine-pyrimethamine should be discontinued if skin eruption, cytopenia, or a bacterial or fungal superinfection occurs. Repetitive administration of the medication to patients with blood dyscrasia and renal or hepatic failure should be performed with caution as the drugs may accumulate to toxic levels.

Pharmacokinetics

Pharmacokinetic parameters of sulfadoxine and pyrimethamine following currently recommended doses for the treatment, seasonal chemoprevention, or intermittent preventive treatment of uncomplicated malaria are summarized in Table 1.

Sulfadoxine and pyrimethamine are readily absorbed from the gastrointestinal tract after oral administration. Plasma protein binding is about 90%, mainly to albumin. The $t_{1/2}$ of sulfadoxine is longer than pyrimethamine (4–11 days and 60–450 h, respectively). The Vd/F of pyrimethamine is about ten times larger than sulfadoxine as it is concentrated in the kidneys, lungs, liver, and spleen. Both sulfadoxine and pyrimethamine cross the placental barrier and pass into breast milk. Both are metabolized by the liver, but enzymes responsible for this biochemical process are not well identified. It is only known that sulfadoxine undergoes varying degrees of acetylation, hydroxylation, and glucuronidation. Renal clearance is the main route of excretion of both drugs.

Factors Associated with Altered Drug Exposure and/or Treatment Response

Children The pharmacokinetics information of sulfadoxine-pyrimethamine in children with malaria has been limited, although it is recognized that the currently recommended mg/kg bw dose of sulfadoxine-pyrimethamine achieves substantially lower plasma drug concentrations in young children than in older patients.

Pregnancy The pharmacokinetics of sulfadoxine and pyrimethamine when administered as a fixed-dose combination are altered in pregnant women. Pregnant patients appear to have higher CL/F and Vd/F of both drugs, resulting in lower AUC and shorter $t_{1/2}$ than nonpregnant adults. These changes in pharmacokinetics may be associated with high rate of treatment failure in pregnant women.

Drug Interactions Clinical effectiveness of sulfadoxine-pyrimethamine is reduced when the drug is given with high-dose folic acid (>5 mg). Concurrent treatment with trimethoprim-sulfamethoxazole should be avoided due to increased risk of severe cutaneous reactions. Additive hematological toxicity may occur when sulfadoxine-pyrimethamine is given in combination with myelosuppressants such as methotrexate, daunorubicin, and cytarabine.

The Vd/F of pyrimethamine is slightly increased when sulfadoxine-pyrimethamine combination is co-administered with artesunate. This interaction is unlikely to be clinically significant as total systemic exposure and plasma concentrations up to day 7 are unaffected.

Atovaquone-Proguanil

Atovaquone-proguanil is currently indicated for malaria prophylaxis. The combination may also be used for treatment of uncomplicated malaria in travelers outside malaria-endemic areas. In addition, it is recommended for use in combination with artesunate and primaquine as an alternative treatment of uncomplicated malaria in areas where WHO recommended treatments are not available or not effective. The atovaquone component was initially developed as a potential antimalarial for monotherapy. It was effective agent with a broad-spectrum antiparasitic activity. A search for combination partner with potential synergy with atovaquone identified the folate inhibitor proguanil as a candidate.

Chemistry and Physical Properties

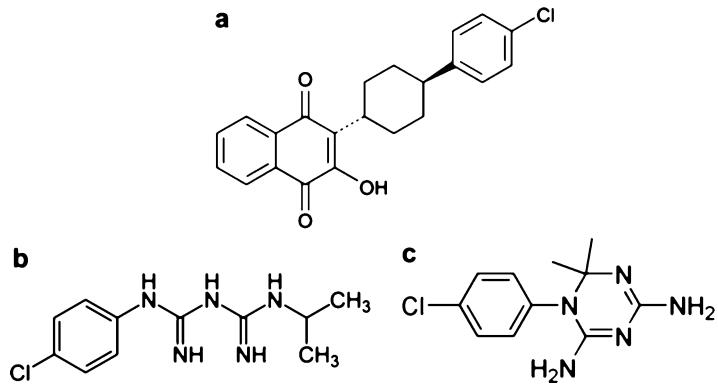
Atovaquone(2-(trans-4-(P-Chlorophenyl)cyclohexyl)-3-hydroxy-1,4naphthoquinone: Fig. 7a) is a hydroxynaphthoquinone with molecular weight of 366.8. Proguanil (*N*-(4-Chlorophenyl)-*n*'-(isopropyl)-imidodicarbonimidic diamide: Fig. 7b), also known as chlorguanide or chloroguanide, is a biguanide compound with molecular weight of 253.7.

Pharmacology

Antimalarial Activities and Mechanism of Action and Resistance Atovaquone is active against all stages of all *Plasmodium* species. It is also active against liver stages, resulting in its utility as a prophylactic drug. However, it is not believed to be active against "dormant" hypnozoites. Atovaquone acts as a competitive inhibitor of ubiquinol, specifically inhibiting the mitochondrial electron transport chain at the bc1 complex. Inhibition of bc1 activity results in a loss of mitochondrial function. Atovaquone exerts potent antimalarial activity with IC_{50} (50% inhibitory concentration) as low as 1–3.5 nM.

Proguanil appears to be active against almost all stages of the malaria parasite life cycle, but clinical use is limited to blood stages. In vivo, it is converted into an active triazine metabolite, cycloguanil (Fig. 7c), which acts by inhibiting parasite's dihydrofolate reductase enzyme, similarly to that of pyrimethamine.

The combination of atovaquone and proguanil acts synergistically. The parent compound, proguanil, rather than the metabolite, cycloguanil, has been demonstrated to synergize the antimalarial activity of atovaquone, lowering the effective concentration at which atovaquone collapses the mitochondrial membrane potential. Atovaquone-proguanil is seldom used in endemic areas because of the propensity for emergence of high-grade resistance to atovaquone. It is well-documented that de novo atovaquone resistance occurs very rapidly. This is due to a missense point mutation at position 268 in the cyt b gene, exchanging tyrosine for serine (Y268S) or, less frequently, asparagine (Y268N). The position 268 in cytochrome b is highly conserved across all phyla and is located within the "ef" helix component of the Qo site, which is putatively involved in ubiquinol binding.



Pharmacology of Antimalarial Drugs, Current Anti-malarials, Fig. 7 Chemical structures of (**a**) atovaquone, (**b**) proguanil, and (**c**) cycloguanil

Other Pharmacological Activities Atovaquone is clinically used for the treatment or prevention of *Pneumocystis carinii* pneumonia (PCP) in patients who are intolerant to trimethoprim-sulfamethoxazole combination. In addition, it is also used for the treatment or prevention of toxoplasmosis and babesia.

Therapeutic Indications for Malaria

Currently, the fixed-dose combination of atovaquone-proguanil is used as a chemoprophylactic agent for preventing malaria in travelers. It may also be considered for the treatment of uncomplicated malaria in travelers outside malaria-endemic areas and for use in combination with artesunate and primaquine as an alternative treatment for uncomplicated malaria, where WHO recommended treatments are not available or not effective.

Adverse Reactions and Toxicity

Atovaquone-proguanil is generally well tolerated with mild adverse reactions. Common adverse reactions include headache, cough, and gastrointestinal disturbance (nausea, vomiting, diarrhea, and abdominal pain). Dizziness, oral ulceration, blood disorders (neutropenia and anemia), and skin reactions (photosensitivity rash and erythema multiforme) rarely occur. Other adverse reactions which are occasionally reported are elevated levels of liver enzymes, hepatitis, hepatic failure, allergic reactions (anaphylaxis, angioedema, Stevens-Johnson syndrome, and vasculitis), and pancytopenia in patients with severe renal impairment. A significant concern for the antimalarials targeting the parasite bc1 including atovaquone is host mitochondrial toxicity. In animal models, this manifested itself as acute toxicity (presumed to be cardiotoxicity).

Contraindications

Atovaquone-proguanil is contraindicated in patients with known hypersensitivity reactions to atovaquone or proguanil or structurally related compounds. Due to increased risk of pancytopenia, it is contraindicated for use as malaria prophylaxis in patients with severe renal insufficiency.

Caution

The doses of atovaquone-proguanil should be selected cautiously in elderly, based on hepatic, renal, or cardiac function, propensity of higher systemic exposure to cycloguanil, and a greater frequency of concomitant disease or concomitant drug therapy.

Pharmacokinetics

The pharmacokinetic parameters of atovaquone in the currently utilized formulation (Malarone^{TM}: 250 mg atovaquone/100 mg proguanil) for malaria prophylaxis and treatment are summarized in Table 1.

Atovaquone exhibits dose-limiting absorption with maximum absorption observed using 750 mg tablets. Poor drug solubility is suggested as the cause of this limited absorption. Furthermore, a marked interpatient variability of atovaquone bioavailability is reported (107%), which is likely due to low drug solubility and the effects of food. The absorption of atovaquone from the gastrointestinal tract is increased by about fourfold when atovaquone is taken with a high-fat meal (two slices of toast with 56 g of butter). The drug is therefore recommended to be taken with a high-fat meal. There is no unexpected accumulation of atovaquone following repeated administration. Proguanil is readily absorbed from the gastrointestinal tract reaching C_{max} within approximately 5 h of administration.

Atovaquone and proguanil are, respectively, 99%and 75% bound to plasma proteins with high affinity to albumin. The long $t_{1/2}$ of 2–3 days is characterized by the enterohepatic circulation. The low drug clearance rate suggests that atovaquone may also accumulate in tissues, where it is protected from biliary clearance. Elimination is primarily via the liver, with almost undetectable amounts (0.6%) of the parent drug being eliminated via the kidneys. More than 90% of the drug excreted in bile (and feces) is in the parent form.

Proguanil undergoes bioactivation by CYP2C19 to the active metabolite, cycloguanil (Fig. 7c). Cycloguanil inhibits *Plasmodial* dihydrofolate reductase and influences DNA synthesis. Proguanil is also further inactivated by

CYP2C19 and to a lesser extent CYP3A4 to 4-chlorophenylbiguanide. The urinary proguanil-cycloguanil metabolic ratio serves as a marker for differential CYP2C19 metabolic activity. Renal excretion of proguanil is about 40 and 60% of the administered dose.

Factors Associated with Altered Drug Exposure and Treatment Response

Children The CL/F values of both atovaquone and proguanil are related to body weight. While most of the pharmacokinetics of proguanil and cycloguanil are comparable in adults and children, the $t_{1/2}$ of atovaquone is shorter in children.

Pregnancy The plasma concentrations of atovaquone and proguanil in pregnant women in the second and third trimesters are approximately half of nonpregnant adults (with and without acute malaria) as a result of expansion of Vd/F and increase of CL/F.

Body Weight Based on the population-based pharmacokinetic analysis, the CL/F of atovaquone has been shown to be increased in patients with higher body weights (60% increase in an 80 kg compared with a 40 kg patient). The CL/F of atovaquone appears to be higher in oriental (8.49 L/h) and Malay (9.13 L/h) subjects compared with Caucasian (1–7.6 L/h) subjects.

Genetic Polymorphism in Drug-Metabolizing Enzymes The association between *CYP2C19* gene polymorphism and variation in proguanil and cycloguanil plasma concentrations has given rise to the hypothesis that patients with poor metabolizer phenotype are at greater risk of treatment failure. The prevalence of the poor metabolizer phenotype varies substantially among ethnics, and two variant alleles, *CYP2C19*2* and *CYP2C19*3*, are largely associated with the poor metabolizer phenotype. Studies in African and Asian populations, however, have not revealed an association between proguanil CYP2C19 metabolic status and treatment or prophylaxis responses as well as the incidence of adverse reactions (mainly gastrointestinal). Based upon these observations, it is proposed that the parent compound proguanil may have a significant intrinsic efficacy independent of its main metabolite cycloguanil. Another plausible explanation may be that undefined metabolite other than cycloguanil, through another metabolic pathway, is responsible for the proguanil efficacy in poor metabolizers.

Drug Interactions The pharmacokinetics of atovaquone and proguanil and its metabolite cycloguanil are unchanged when given as atovaquone-proguanil combination. There is in vitro evidence of possible inhibition of CYP3A4 by atovaquone. Plasma/serum concentrations of aceprometazine, alimemazine, chlorproethazine, chlorpromazine, and etoposide can be increased when co-administered with atovaquone. The risk of QTc prolongation can be increased when atovaquone is combined with artemether.

Pharmacokinetic interactions between atovaquone and antiretrovirals have been reported. Efavirenz, lopinavir, ritonavir, and saquinavir (all highly protein-bound drugs) reduced atovaquone plasma concentrations in HIV-infected patients. On the other hand, a recent case study described an HIV-infected female with a marked increase in plasma concentrations of the antiretrovirals etravirine (55%) and saquinavir (274%), but not raltegravir following atovaquone-proguanil prophylaxis. Atovaquone has been shown to inhibit the glucuronidation of zidovudine. Co-administration of atovaquone and the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine increased the exposure (33% increase in AUC) and decreased the oral clearance (25%) of zidovudine in HIV-infected patients. Furthermore, patients taking atovaquone showed a trend toward lower zidovudine/glucuronide plasma concentrations (6% decrease in AUC) and a significant decrease in the ratio between zidovudine/glucuronide and plasma concentrations (30% decrease). Atovaquone exposure itself was unchanged. The increased zidovudine plasma concentrations and reduced zidovudine glucuronidation may potentially lead to increased formation of the CYP450-mediated zidovudine

metabolite 3-amino-3deoxythymidine, which shows a sevenfold higher toxicity in bone marrow cells compared with the parent drug. Caution is advised in patients taking additional drugs with similar toxicity profiles to zidovudine, particularly hematological toxicity.

Plasma concentration of atovaquone is reduced when given concurrently with metoclopramide and tetracycline. Atovaquone exposure (AUC) has been shown to be markedly decreased (50%) in patients with *Toxoplasma gondii* infection concurrently treated with the anti-TB drug rifampicin but to a lesser extent (34%) with rifabutin. The concomitant administration of atovaquone and rifampicin is therefore not recommended as rifampicin is a potent inducer of CYP2C19, and it therefore could affect proguanil antimalarial activity.

Atovaquone causes an increase in free warfarin concentrations to super-therapeutic levels. Lack of pharmacokinetic interactions is reported between atovaquone and the anticonvulsant phenytoin.

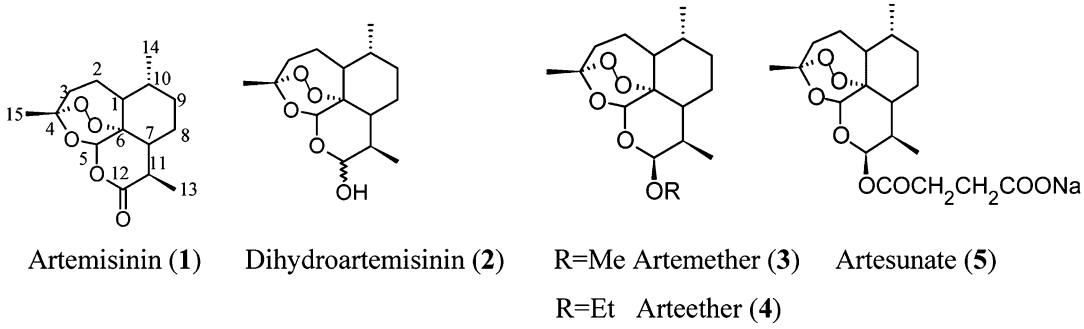
Proguanil may potentiate warfarin action but may reduce effectiveness of live typhoid vaccine. The conversion of proguanil to cycloguanil is reduced in the presence of estrogen. Proguanil and cycloguanil have been shown to inhibit P-glycoprotein-mediated taxol transport without being substrates for P-glycoprotein. Interactions between these compounds and other substrates of P-glycoprotein would be expected.

Artemisinin and Derivatives and Artemisinin-Based Combination Therapies (ACTs)

Artemisinin drugs, originated from the Chinese herb qinghao (Chinese wormwood *Artemisia annua* L.), belong to a unique class of compounds, sesquiterpene lactone endoperoxide, and are new generation of potent antimalarials. Qinghaosu has been used for over 2000 years in Chinese traditional medicine for the treatment of fever. Its antimalarial application was first described in the *Handbook of Prescriptions for Emergencies* in the middle of the fourth century in China. The herb was used as a tea for treatment of malaria in China for over 1500 years. Artemisinin (quinghaosu) is the principal compound isolated from *A. annua* and is further derivatized to the more active (four- to fivefold) derivatives, i.e., artesunate, β-arteether, and dihydroartemisinin. Dihydroartemisinin is also an active human plasma metabolite of artesunate and artemether. Artemisinin derivatives have constituted the key antimalarials that play an essential role in the control of malaria since the emergence and widespread of multidrug-resistant *P. falciparum* malaria. Currently, artesunate, artemether, and dihydroartemisinin are in clinical uses for treatment of malaria, either as monotherapy (for severe malaria) or as components of artemisinin-based combination therapies (ACTs) for uncomplicated malaria. ACTs are currently the most powerful strategy to treat malaria and prevent malaria-related deaths. With this successful discovery of artemisinins, Professor Tu was awarded the Nobel Prize in Physiology or Medicine in 2015 for the discovery of this effective antimalarial compound.

Chemistry and Physical Properties

Artemisinin (Fig. 8) is a sesquiterpene lactone peroxide with a characteristic endoperoxide moiety essential for antimalarial activity. Artemisinin is poorly soluble in water. Artesunate is a water-soluble hemisuccinate ester which can be administered by intravenous and intramuscular injection. It is a colorless needle crystal or white crystalline powder, odorless, and almost tasteless. Artesunate can be dissolved in sodium bicarbonate solution, forming water-soluble sodium salt. Artemether and arteether (Fig. 8) are the methyl and ethylethers of dihydroartemisinin (Fig. 8) which possess physical and chemical properties similar to artemisinin. Both are easily soluble in a variety of organic solvents such as ethanol, acetone, and chloroform. Both ethers have the advantage of being more oil soluble than artemisinin.



Pharmacology of Antimalarial Drugs, Current Anti-malarials, Fig. 8 Chemical structures of artemisinin and derivatives

Artemisinin and its derivatives decompose in protic solvents other than water. Artesunate is more water soluble than other artemisinins and therefore can be administered intravenously. Artemisinin drugs also show a remarkable thermal instability. The derivatives are more unstable than artemisinin. The drugs should be stored in air-tight containers in a cool place below 25°C and protected from light. Molecular weights of artemisinin, artemether, β-arteether, and artesunate are 280, 296, 312, and 404, respectively.

Pharmacology

Antimalarial Activities and Mechanisms of Action and Resistance

Artemisinin drugs have broad stage specificity against blood stage parasites from the ring stage to early schizonts. They are also active against the early gametocide stages but inactive against extra-erythrocytic forms, sporozoites, liver schizonts, and merozoites.

Artemisinin drugs are rapidly acting blood schizontocidal antimalarials against either chloroquine-sensitive or chloroquine-resistant *P. falciparum*, *P. vivax*, *P.* ovale, and *P. malariae*. Their potent gametocytocidal activities reduce gametocyte carriage and therefore limit malaria transmission from the treated infection. The artemisinin compounds stop parasite development rapidly, thereby preventing subsequent cytoadherence and rosetting (both are thought to be important pathophysiological mechanisms in severe malaria). Fever and parasites are more rapidly cleared than other antimalarials. Defervescence occurs within 1–2 days, and parasitemia disappears within 2–3 days after drug administration. About 90% clearance of asexual erythrocytic parasitemia is usually observed within 24 h. Total dose and duration of drug administration have an influence on the cure rate. Correlation between dosage regimen (total dose and duration), severity of the disease, and cure rate has been reported. The longer the duration of treatment, and/or the lesser the severity of the infection, the higher is the cure rate.

Currently, artemisinin monotherapy (artesunate and artemether) is only used for initial treatment of severe malaria but is not recommended for treatment of uncomplicated malaria due to widespread of multidrug-resistant *P. falciparum* and the necessity for prolonged treatment regimens. For this purpose, they are typically used in combination with other structurally unrelated antimalarial drugs as ACTs. ACTs are co-formulations of a fast-acting, highly potent artemisinin and a slow-acting, less-potent partner drug (e.g., mefloquine, piperaquine, and lumefantrine) that are given orally over 3 days. During their short half-life, artemisinins leave only residual parasites, which are further eradicated by the slowly eliminated partner drug. The combination is also believed to inhibit the selection of de novo artemisinin-resistant mutants.

Artemisinin is a sesquiterpene lactone containing a peroxide bridge that plays an essential role in antimalarial effects. The precise molecular targets of action of artemisinins are not well

understood, but the prevailing theory is the cleavage of the endoperoxide bridge which leads to the formation of reactive carbon radicals that subsequently alkylate essential biomolecules of malaria parasites. A previously proposed molecular mechanism of action for artemisinins is the inhibition of the malarial parasite's calcium ATPase (sarcoplasmic/endoplasmic reticulum calcium ATPase, SERCA). More recent investigations suggest newly identified protein targets in broad pathways involved in the glycolysis, hemoglobin degradation, antioxidant defense, and protein synthesis, processes essential for parasite survival.

The emergence of *P. falciparum* resistance to artemisinin and derivatives has recently developed in the Greater Mekong Subregion (GMS: China, Cambodia, Laos PDR, Myanmar, Thailand, and Vietnam). This worrisome development threatens to make malaria practically untreatable in this region and threatens to compromise global endeavors to eliminate this disease. Initial widespread use of artemisinins as monotherapy in the GMS is likely to be the key factor that contributes to their reduced efficacy and/or resistance reported in recent years along the Thai-Cambodian and Thai-Myanmar borders. Artemisinin resistance is characterized as a delay in parasite clearance time. Partial resistance to artemisinin in *P. falciparum* was first reported in 2008, in Battambang Province in western Cambodia. It was subsequently confirmed in 2009, in Pailin Province, the well-known epicenter of antimalarial multidrug resistance. Artemisinin resistance has since been reported elsewhere in western Cambodia, western Thailand, southern Myanmar, Southern Vietnam, and China.

A recent series of clinical, in vitro, genomics, and transcriptomics studies in the GMS has shown that artemisinin resistance manifests as slow parasite clearance in patients and increased survival of early ring-stage parasites in vitro. The molecular mechanism underlying this resistance phenotype is single-nucleotide polymorphisms in the parasite's *"K13*" gene. The *K13* propeller gene is located on chromosome 13 and encodes a kelch protein. The mutation is associated with an upregulated "unfolded protein response" pathway that may antagonize the prooxidant activity of artemisinins and in addition the selection of resistance in *P. falciparum* against the partner drug.

Other Pharmacological Activities

Apart from antimalarial activities, artemisinin drugs have also been shown to exhibit a wide range of pharmacological actions against viruses, helminthes, fungi, and even a variety of cancer cells. In addition, they also possess anti-inflammatory and immunosuppressant activities.

In vitro and in vivo studies demonstrated activities of artemisinin and derivatives against other protozoas (*Leishmania* spp., *Trypanosoma* spp., *Toxoplasma gondii*, *Neospora caninum*, *Eimeria tenella*, *Acanthamoeba castellanii*, *Naegleria fowleri*, *Cryptosporidium parvum*, *Giardia lamblia*, *Babesia* spp.), helminths (*Schistosoma* species and *Fasciola hepatica*), fungi (e.g., *Cryptococcus neoformans*), and viruses (e.g., human cytomegalovirus).

Artemisinins exert selective cytotoxic effects against a wide range of cancer types both in vitro and in vivo. These effects appear to be mediated by artemisinin-induced changes in multiple signaling pathways, interfering simultaneously with multiple hallmarks of cancer (cell cycle arrest, apoptosis, angiogenesis, and cancer invasion and metastasis). Results from a limited number of clinical trials in some types of cancer also support their anticancer property.

Artemisinins have been evaluated in animal models of autoimmune diseases, allergic disorders, and septic inflammation. Their potent anti-inflammatory effects have been attributed to the regulation of both innate and adaptive immunity. Artemisinin family drugs can suppress T-cell activation both in vitro and in vivo. In addition, they have been shown to inhibit Toll-like receptors, Syk tyrosine kinase, phospholipase Cγ, PI3K/Akt, MAPK, STAT-1/3/5, NF-κB, Sp1, and Nrf2/ARE signaling pathways. Artemether suppresses T-cell proliferation and IL-2 production in response to TCR engagement or mitogens in vitro.

Therapeutic Implications for Malaria

Uncomplicated Malaria

The artemisinins rapidly relieve signs and symptoms of acute malaria by rapidly clearing parasitemia. Parasite numbers is reduced by 100- to 1000-fold *per* asexual cycle of the parasite (a factor of approximately 10,000 in each 48-h asexual cycle). This action is fastest among the currently available antimalarial drugs. Because artemisinin and its derivatives are eliminated rapidly, when given alone, a 7-day course of treatment is required. In 2001, the WHO initially recommended the use of ACTs as first-line treatment of uncomplicated malaria in areas where the parasites were resistant to monotherapy with other drugs including chloroquine, sulfadoxine-pyrimethamine, and mefloquine. This recommendation was extended to the entire malaria-endemic areas of the world in 2006, and the use of artemisinin in monotherapy was banned to prevent the selection of artemisinin-resistant parasites. In 2012, five different 3-day ACTs, including dihydroartemisinin-piperaquine, artesunate-mefloquine, artemether-lumefantrine, artesunate-sulfadoxine-pyrimethamine, and artesunate-amodiaquine, were deployed in 79 countries with endemic malaria. The concept of combination therapy relies on the rapid onset of schizonticidal action of artemisinins to rapidly reduce parasitemia, leaving the residual parasitemia to be cleared by high concentrations of the partner drugs. This results in the protection of artemisinin by its partner drug from developing resistance and vice versa. An additional advantage from a public health perspective is the ability of the artemisinins to reduce gametocyte carriage and, therefore, the transmissibility of malaria. This contributes to malaria control, particularly in areas of low-to-moderate endemicity. Shorter courses (1–2 days) are not recommended as they are less effective, have less effect on gametocytes, and provide less protection for the slowly eliminated partner drug.

Currently (since 2015), these five ACTs are currently recommended by the WHO for treatment of uncomplicated malaria in all endemic areas in the following clinical situations:

(i) Treatment of children and adults with uncomplicated *P. falciparum* malaria except the first-trimester pregnant women. The ACTs can be used safely in pregnant women during the second and third trimesters.
(ii) Nonimmune travelers with uncomplicated *P. falciparum* malaria returning to non-endemic settings.
(iii) An alternative treatment to chloroquine in adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae*, or *P. knowlesi* in areas with chloroquine-sensitive infections.
(iv) First-line treatment of adults and children with chloroquine-resistant *P. vivax*, as well as *P. ovale*, *P. malariae*, or *P. knowlesi*.

The choice of ACTs in a country or region should be based on background of drug resistance (particularly of the partner drugs), optimal efficacy, safety, and patients' compliance. Fixed-dose combinations rather than co-blistered or loose, single-agent formulations are recommended whenever possible. For young children and infants, pediatric formulations, with a preference for solid formulations rather than liquid formulations, are recommended.

Resistance of *P. falciparum* to the currently used ACTs has now emerged and is following a similar pattern of resistance previously observed with other antimalarial drugs. Thus far, studies have documented evidence of *P. falciparum* resistance to artemisinins in five countries of the GMS, i.e., Cambodia, Laos, Myanmar, Thailand, and Vietnam, and this was confirmed on the Cambodia-Thailand border. It is therefore, crucial to monitor the efficacy and safety of newly formulated ACTs in view of artemisinin resistance.

Clinical uses of the currently used ACTs are as follows:

(i) *Artemether-lumefantrine*

The combination is available as dispersible or standard tablets containing 20 mg artemether and 120 mg lumefantrine (the flavored dispersible pediatric formulation facilitates use in young

children) or as *s*tandard tablets containing 40 mg artemether and 240 mg lumefantrine in a fixed-dose combination formulation. The advantage of this ACT is that the combination partner, lumefantrine, is not available as monotherapy and has never been used alone for malaria treatment. The recommended adult dose regimen is artemether-lumefantrine given twice a day at a total six doses for 3 days (four tablets *per* dose). The patient should receive the initial dose, followed by the second dose 8 h later, and then one dose twice daily for the following 2 days. The drug should be taken immediately after food or fat-containing drink (e.g., milk) particularly in the second and third days of treatment.

(ii) *Artesunate-amodiaquine*

The combination is available as a fixed-dose combination in tablets containing 25/67.5 mg, 50/135 mg, or 100/270 mg of artesunate-amodiaquine. A total therapeutic dose range of 6–30 mg/kg bw *per* day artesunate and 22.5–45 mg/kg bw *per* day amodiaquine for 3 days is recommended.

(iii) *Artesunate-mefloquine*

The combination is available as a fixed-dose formulation of pediatric tablets containing 25 mg artesunate and 55 mg mefloquine hydrochloride (50 mg base) or adult tablets containing 100 mg artesunate and 220 mg mefloquine hydrochloride (200 mg base). A total therapeutic dose of 4 (2–10) mg/kg bw *per* day artesunate and 8.3 (5–11) mg/kg bw *per* day mefloquine, given once a day for 3 days, is recommended. to reduce vomiting, mefloquine dose should be split over 3 days, as in current fixed-dose combination.

(iv) *Dihydroartemisinin-piperaquine*

The combination is available as a fixed-dose combination in tablets containing 40 mg dihydroartemisinin and 320 mg piperaquine and a fixed-dose combination pediatric tablets containing 20 mg dihydroartemisinin and 160 mg piperaquine. The recommended dose regimen for adults and children weighing >25 kg is a total dose of 4 (2–10) mg/kg bw *per* day dihydroartemisinin and 18 (16–27) mg/kg bw *per* day piperaquine given once a day for 3 days. In children aged <25 mg/kg, a minimum of 2.5 mg/kg body weight *per* day of dihydroartemisinin and 20 mg/kg bw *per* day of piperaquine for 3 days is recommended.

(v) *Artesunate-sulfadoxine-pyrimethamine*

The combination is available in blister-packed, scored tablets containing 50 mg artesunate and fixed-dose combination tablets containing 500 mg sulfadoxine/25 mg pyrimethamine. There is no fixed-dose combination. A total therapeutic dose of 4 (2–10) mg/kg bw *per* day artesunate given once a day for 3 days and a single administration of at least 25/1.25 (25–70/1.25–3.5) mg/kg bw *per* day sulfadoxine-pyrimethamine, given once a single dose on day 1, are recommended. Clinical use of this ACT should be avoided in uncomplicated *P. falciparum* malaria patients coinfected with HIV/AIDS if they are being treated with the antiretroviral drugs efavirenz or zidovudine. The disadvantage of this ACT is that it is not available as a fixed-dose combination, which may compromise patients' adherence and increase the risk for distribution of loose artesunate tablets, despite the WHO ban on artesunate monotherapy. Resistance is likely to be increased with continued widespread use of sulfadoxine-pyrimethamine, sulfalene-pyrimethamine, and cotrimoxazole (trimethoprim-sulfamethoxazole). Its use is restricted to areas where sulfadoxine-pyrimethamine is still active, which excludes all of Southeast Asian countries, most of South American, East African, and West African countries.

(vi) *Artesunate-pyronaridine*

Apart from the five WHO recommended ACT is another EMA (European Medicines Agency) recommended, US FDA approved, and WHO pre-qualified and on the list of Essential Pediatric

Medicines of WHO. The combination is available as film-coated tablets (Pyramax™, developed by Shin Poong Pharmaceutical, China, University of Iowa, USA, and MMV). Each tablet contains 180 mg pyronaridine tetraphosphate and 60 mg artesunate). Artesunate-pyronaridine combination is indicated in the treatment of acute, uncomplicated malaria infection caused by *P. falciparum* or *P. vivax* in adults and children weighing 20 kg or more. A total therapeutic doses ranging from one to four tablets given once a day for 3 days are recommended. A granule formulation is available for children weighing between 5 kg and under 20 kg.

Severe Malaria

Parenteral artesunate is recommended for treatment of severe malaria. While the possible risk for teratogenicity limits the use of artemisinin drugs in the treatment of uncomplicated malaria in pregnant women in the first trimester, treatment of severe malaria is recommended as it is potentially lifesaving for the mother. Compared to quinine, artemisinins treatment in the first trimester is not associated with an increased risk of miscarriage or stillbirth. No difference in the prevalence of major congenital anomalies is observed, although available data have been limited. The benefits of using artemisinins to treat malaria in early pregnancy are likely to outweigh the adverse outcomes of partially treated malaria.

Artemether did not prove to be better than quinine on survival rate, and artesunate is the first choice in low-transmission areas. Intravenous or intramuscular artesunate at 2.4 mg/kg bw *per* dose is strongly recommended in adults and children with severe malaria (including infants, pregnant women in all trimesters, and lactating women) for at least 24 h until they can tolerate oral medication and then followed by a 3 days ACT (with a single-dose primaquine in areas with low transmission). Alternatively, a simplified three doses of 4 mg/kg bw intravenous artesunate (given at 0, 24, and 48 h) instead of five doses of 2.4 mg/kg are recommended. In children weighing lower than 20 kg, a higher dose of artesunate (3 mg/kg bw *per* dose) is strongly recommended to ensure equivalent exposure to the drug.

If artesunate is not available, artemether in preference to quinine is recommended for both children and adults with severe malaria. In situations where complete treatment of severe malaria is not possible but injections are available, a single intramuscular dose of artesunate (if not available, intramuscular artemether or quinine) is strongly recommended in adults and children with severe malaria before transferal to an appropriate facility for further care. Where intramuscular artesunate is not available, a single rectal dose of 10 mg/kg bw of artesunate is strongly recommended in children aged lower 6 years (do not use in older children and adults) before transferal to an appropriate facility for further care.

Adverse Reactions and Toxicity

Artemisinin drugs are generally well tolerated after both oral- and parenteral-dose administration in humans. Post-artemisinin delayed hemolysis is commonly found with artemisinins when used for treatment of severe malaria. Although no deaths have been reported so far, this serious adverse reaction may lead to life-threatening anemia. Preclinical studies showed considerable toxicity of artemisinin drugs at high doses particularly the central nervous system and liver function abnormalities and reduction in the reticulocyte counts. Most of the effects returned to normal within 48 h. Nevertheless, large clinical studies and meta-analyses do not show serious adverse effects in humans. The inconsistencies of results of the preclinical and clinical studies are explained by the relationship between pharmacodynamics (toxic effects) and plasma concentrations of artemisinin drugs and active metabolite dihydroartemisinin. Most of the observed serious toxicity in experimental animals is acute toxicity associated with long-term rather than acute drug exposure. Rapid elimination of artemisinin drugs after oral-dose administration represents a relatively safe route of administration compared to delayed drug release after intramuscular injection. Furthermore, there are drug-related differences in toxicological profiles of artemisinins. Intramuscular application of artemether or -arteether, but not to artesunate, is

safe and profiles acceptable plasma concentration-time profiles following intramuscular administration in severe malaria.

Adverse reactions of artemisinins that may occur in clinical uses include hypersensitivity reactions (estimated risk of 1 in 3000), mild gastrointestinal disturbance, dizziness, reticulocytopenia, and elevated liver enzyme activity. Although no ECG abnormalities have been found in most studies, bradycardia and very slight prolongation of the QTc interval have been reported. While studies in experimental animals show neurotoxicity after parenteral artemether, clinical, neurological, and pathological studies in humans have not shown similar findings.

In experiment animals, dose-dependent fetal toxicity was observed after administration of artesunate in the first trimester and was more likely to occur with increased duration of treatment. However, there is no evidence that artemisinin derivatives are teratogenic in humans, but experience is limited.

Artemether-lumefantrine and dihydroartemisinin-piperaquine are the most intensively studied antimalarial drugs with regard to cardiotoxicity. Artemether-lumefantrine has a wide therapeutic index and is generally well tolerated. Common adverse reactions are nausea, dizziness, and headache, which are not easily distinguishable from symptoms of acute malaria. It does not significantly prolong QTc interval. No sudden death has been attributed to cardiotoxicity following artemether-lumefantrine.

Dihydroartemisinin-piperaquine is well tolerated. Common adverse reactions that may occur include nausea, vomiting, diarrhea, anorexia, anemia, dizziness, headache, sleep disturbance, and cough. Although there was no evidence of cardiotoxicity in large randomized trials and extensive use of dihydroartemisinin-piperaquine, the partner drug piperaquine does prolong the QTc interval on ECG (reflecting ventricular repolarization which may cause potentially life-threatening ventricular arrhythmia) by approximately the same magnitude as chloroquine but lower than quinine. One possible sudden cardiac death associated with dihydroartemisinin-piperaquine was reported among 200,000 patients. Dihydroartemisinin-piperaquine was reported to increase the QTc interval by 45.2, 35.5, and 21.0 ms in healthy subjects following the administration of each dose with high (1000 kcal) or low (400 kcal) fat/calorie meal and fasting conditions, respectively. None had a QTc interval greater than 500 ms.

Contraindications

Artemisinin drugs are contraindicated in patients with known hypersensitivity to any artemisinin derivative. All ACTs should not be administered to patients with known hypersensitivity to artemisinins and combination partners. Dihydroartemisinin-piperaquine should not be used in patients with congenital QTc prolongation or who have a clinical condition or are on medication that results in QTc interval prolongation.

Caution

Artemether should not be given to patients with meningitis as a marked increase in the CSF concentrations may occur. Artemether should also be used with caution in patients with acute renal failure due to possible drug accumulation.

Due to limited information on safety profile in patients aged over than 65 years or children weighing less than 5 kg, clinical use of artemether-lumefantrine should be with caution. Similarly, dihydroartemisinin-piperaquine should be used in patients aged over 70 years, infants weighing lower than 5 kg, and patients with renal or hepatic impairment with special caution in view of the lack of evidence on the safety profiles of the drug in these groups.

Although there is no evidence for iatrogenic toxicity of artemether-lumefantrine in patients with congenital or clinical conditions resulting in QTc prolongation, a family history of congenital long QT syndrome or sudden death, electrolyte abnormalities such as hypokalemia or hypomagnesemia, the drug should not be used in these patients as it may affect cardiac conductivity.

Pharmacokinetics

The pharmacokinetic parameters of artemether (when given by intramuscular injection for treatment of severe malaria) and artesunate (when

given by intravenous injection, intramuscular injection, and rectal route for severe malaria, as well as oral route for uncomplicated malaria) together with their active plasma metabolite dihydroartemisinin are summarized in Table 1.

Artesunate (water soluble) is suitable for administration by all routes, while artemether (water insoluble, lipid soluble) can be administered by intramuscular, oral, or rectal (suppository) route. Artemether (lipid soluble) is currently available for clinical use as oral and intramuscular formulations. Oral dihydroartemisinin is currently in clinical use as co-formulation with piperaquine (ACT). The rectal administration has emerged as one of the important routes, especially in tropical countries where it can be lifesaving. Nevertheless, there is large interindividual variation in the drug bioavailability.

Artemisinin and derivatives exhibit unique and highly variable pharmacokinetic properties. All are rapidly absorbed and eliminated. The $t_{1/2}$ is short ranging from 0.5 to 4 h. T_{max} of artemisinin drugs vary from minutes to hours, depending on the drug formulation and route of administration. Bioavailability of artemisinin drugs is also highly variable (<25–>85%), depending on the drug formulation, route of administration, health status, and the nature of malaria infection. The bioavailability of oral artesunate and artemether following oral-dose administration is as low as low 30% due to high first-pass metabolism. Oral artemether peaks in about 2–6 h. Oral dihydroartemisinin is rapidly absorbed from the gastrointestinal tract with marked interindividual variation. T_{max} is achieved at about 1–2 h.

Following an intravenous injection of artesunate, high initial plasma concentration is observed and is subsequently rapidly declined. Dihydroartemisinin concentration reaches t_{max} within 9–20 min after artesunate dosing. Intramuscular artesunate produces lower C_{max} of artesunate and delayed t_{max} of dihydroartemisinin. Following oral administration, C_{max} of artesunate and dihydroartemisinin are achieved within 1 and 1–2 h, respectively. Following rectal administration, pharmacokinetics of artesunate and dihydroartemisinin are similar to oral artesunate, except delayed t_{max} of artesunate. Intramuscular artemether is absorbed slowly and erratically.

Plasma protein binding of artemisinin drugs ranges from 43% to 95% (44–93%, 93%, and 95% for dihydroartemisinin, artesunate, and artemether, respectively). Artesunate and artemether are extensively converted to the active plasma metabolite dihydroartemisinin which accounts for most of antimalarial activity. High concentrations can be found in the bile, liver, and kidney.

Artesunate and artemether are rapidly (within 15 min of dosing) metabolized in the liver to form the active metabolite dihydroartemisinin by CYP2A6, CYP3A4/A5, and CYP3A4 (secondary contribution of CYP2B6 and CYP3A5), respectively. Artesunate is biotransformed into its active plasma metabolite dihydroartemisinin by plasma esterases with possible contribution of CYP2A6. Dihydroartemisinin is rapidly inactivated to dihydroartemisinin-β-glucuronide by the phase II enzymes UGT1A9 and UGT2B7. The $t_{1/2}$ of dihydroartemisinin is approximately 1–2 h. Evidence also suggests rapid elimination of artesunate (in minutes) and artemether (1–11 h). The concentration of artemether parent compound predominates after intramuscular artemether in severe malaria patients.

Several artemisinin drugs are subject to autoinduction of the hepatic first-pass metabolism, resulting in a decline in bioavailability after repeated dosing, which might compromise treatment. Artemether and dihydroartemisinin including artemisinin have been shown to induce CYP3A activity. Artemisinin and -arteether also activate CYP2C19, and artemisinin upregulates CYP2B6. In vitro experiments using primary human hepatocytes and in a human intestinal cell line suggest that activation of the xenosensors pregnane X receptor (PXR) and constitutive androstane receptor (CAR) is the underlying mechanism on CYP450 induction by artemisinins. Artesunate and artemisinin have been shown not to interact with P-glycoprotein (MDR1)-mediated taxol transport in $Caco_2$ cells or with MRP1 and BCRP in multidrug-resistant cells. Likewise, in rats, P-glycoprotein did not

contribute to intestinal absorption or inducible pharmacokinetics of artemisinin.

Factors Associated with Altered Drug Exposure and/or Treatment Response

Variation of artemisinin pharmacokinetics between individuals of up to 50-fold has been reported in both healthy subjects and malaria patients. This variation, however, does not correlate with clinical outcome; similar parasite and fever clearance rates are observed in all malaria patients regardless of clinical outcome. The partner drugs as components of the ACTs may mask any potential artemisinin drug failures. There is evidence that pregnancy per se, malaria infection, and race/ethnicity can alter the pharmacokinetic properties of the ACT components.

Genetic Polymorphisms of Drug-Metabolizing Enzymes and Transporters

The genetic basis of such a large interindividual pharmacokinetic variability of artemisinin drugs has not clearly been addressed. Phenotypic consequences of polymorphisms in drug-metabolizing enzymes CYP2B6 and UGT2B7 and transport proteins (particularly P-glycoprotein) on the pharmacokinetics and effectiveness of artemisinin drugs are yet to be determined. This is particularly important in view of high prevalence of *CYP2B6* functional polymorphisms in several malaria-endemic countries.

Pregnancy

Pregnancy has been reported to alter the pharmacokinetic properties of artemisinin drugs as well as different components of the ACTs. Plasma C_{max} and AUC of oral dihydroartemisinin have been shown to be lower in pregnant women compared with nonpregnant women. Results of a more recent systematic analysis show lower C_{max} and exposure (AUC) of dihydroartemisinin after oral administration of artemether, artesunate, and dihydroartemisinin in women in the second and third trimesters of pregnancy. With regard to the ACT combination partners, relatively low day 7 plasma concentrations of lumefantrine are commonly found following artemether-lumefantrine combination, indicating a low drug exposure. The influence of pregnancy on amodiaquine and piperaquine appears not to be clinically relevant. Sulfadoxine plasma concentration is significantly reduced, and clearance rate is higher in pregnancy. For pyrimethamine and mefloquine, available data regarding pharmacokinetic changes in pregnancy have been limited. Lower concentrations achieved in pregnant women may lead to reduced clinical efficacy and increased morbidity and mortality. Higher failure rates have been shown in pregnant women with both artemether and artesunate. Although the exact mechanism is unknown, these discrepancies may be due to pharmacokinetic changes of both drugs that occur in pregnancy such as increases in the CL and Vd. It is essential that dose-optimization studies of ACTs are performed in pregnant women, in order to maximize the clinical efficacy and tolerability of these regimens.

Metabolic Auto-induction

Several artemisinin drugs suffer from auto-induction of the hepatic first-pass metabolism, resulting in a decline of bioavailability after repeated doses. The pharmacokinetics of the artemisinin drugs have been shown to exhibit an unusual time dependency during a 7-day oral daily regimen.

Renal Disease

Pharmacokinetics of artemether is changed in patients with acute with increased C_{max}, AUC, while decreased Vd and longer $t_{1/2}$ compared with nonrenal failures. Artemether should be used with caution in patients with acute renal failure due to concern about drug accumulation.

Interaction Between Artemisinins and Other Drugs

Artemisinin and derivatives induce CYP2B6 and CYP2C19, CYP3A (3A4/3A5), and CYP2A6 and inhibit CYP1A2. Clinical studies with the most commonly used ACTs, artemether-lumefantrine, artesunate-mefloquine, and artesunate-amodiaquine, have so far not shown any clinical significant interactions. Tafenoquine co-administration (as gametocytocide or tissue schizonticide) had no clinically relevant effects on dihydroartemisinin, piperaquine, artemether, or lumefantrine

pharmacokinetics. The pharmacokinetics of artemether, dihydroartemisinin, or mefloquine are not significantly changed when oral artemether is given with mefloquine. Artesunate does not influence atovaquone or proguanil pharmacokinetics, and the triple-drug combination of atovaquone, proguanil, and artesunate is well tolerated.

Drug Interactions of ACTs

Artemether-lumefantrine: Absorption of the hydrophobic lipophilic lumefantrine component of artemether-lumefantrine combination varies widely between individuals and is greatly enhanced with fat co-administration. Decreased exposure to lumefantrine has been documented in young children (<3 years), pregnant women, large adults, smokers, and patients co-administered with mefloquine, rifampicin, or efavirenz. These patients should be closely monitored and their full adherence to medication ensured. On the other hand, increased exposure to lumefantrine has been documented in patients co-administered with lopinavir, ritonavir-boosted lopinavir antiretroviral agents, but without increase in toxicity. No dose adjustment is indicated. There is no pharmacokinetic interaction between tafenoquine and artemether-lumefantrine; both can be co-administered safely.

Artesunate-amodiaquine: Treatment failure after amodiaquine monotherapy is more frequent among children who are underweight for their age. Therefore, their response to treatment should be closely monitored. Furthermore, this ACT is associated with severe neutropenia, particularly in patients coinfected with HIV and especially in those on zidovudine and/or cotrimoxazole. Concomitant use of efavirenz increases exposure to amodiaquine and hepatotoxicity. Concomitant use of artesunate-amodiaquine with these drugs should be avoided. No significant changes in the pharmacokinetics of amodiaquine or its metabolite monodesetylamodiaquine have been observed during the second and third trimesters of pregnancy. No dose adjustment is recommended. No effect of age has been observed on the plasma concentrations of amodiaquine and monodesetylamodiaquine. No dose adjustment by age is indicated.

Artesunate-mefloquine: Concomitant use of the anti-TB drug rifampicin with mefloquine may result to a marked decrease in exposure of mefloquine, which may potentially decrease antimalarial efficacy of mefloquine. Patients taking this drug should be followed up carefully to identify treatment failure.

Dihydroartemisinin-piperaquine: Consumption of a high-fat, high-calorie meal markedly increases piperaquine exposure ($AUC_{0\text{-}168h}$). High-fat meal significantly accelerates the absorption of piperaquine, thereby increasing the risk for potentially arrhythmogenic delayed ventricular repolarization (prolongation of the QTc interval). It is therefore a general recommendation that piperaquine-dihydroartemisinin should not be administered at least 3 h before or after food consumption. Malnourished children are at increased risk of treatment failure following treatment with dihydroartemisinin-piperaquine due to decreased plasma concentrations. Their response to treatment should be closely monitored. In pregnant women, dihydroartemisinin and piperaquine exposure are reduced and may increase the risk of treatment failure. In addition, the increase in clearance of piperaquine in pregnancy results in decreased $t_{1/2}$. This may shorten the posttreatment prophylactic effect of dihydroartemisinin-piperaquine combination. However, as this pharmacokinetic change does not affect primary efficacy, no dosage adjustment is recommended. There is no pharmacokinetic interaction between tafenoquine and dihydroartemisinin-piperaquine, and both can be co-administered safely.

Artesunate-sulfadoxine-pyrimethamine: The low dose of folic acid (0.4 mg daily) that is required to protect the fetuses of pregnant women from neural tube defects does not reduce clinical efficacy of sulfadoxine-pyrimethamine. On the other hand, higher dose (5 mg daily) significantly reduces clinical efficacy of sulfadoxine-pyrimethamine, and both drugs should not be given concomitantly.

Interaction Between ACTs and Antiretroviral Drugs

Treatment of malaria in patients coinfected with HIV is a major concern due to potential pharmacokinetic as well as pharmacodynamic

interactions. Several anti-HIV drugs are substrates and/or inhibitors of CYP3A and MDR1 (e.g., protease inhibitors) or CYP2B6 (efavirenz), so there is a potential risk of multiple drug interactions. Artesunate increases plasma concentration of nevirapine. Artemether plasma concentration is increased with ketoconazole but decreased with darunavir/ritonavir, lopinavir/ritonavir, nevirapine, efavirenz, etravirine, and rifampicin.

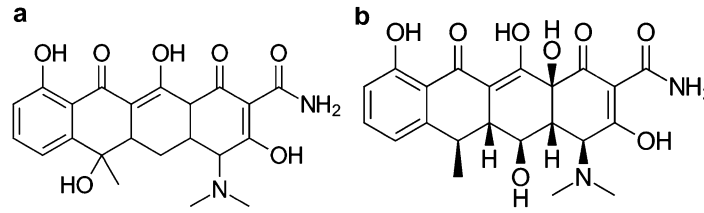
With regard to the interaction between the ACTs and antiretroviral drugs, the protease inhibitors (PIs) tend to increase the exposure of lumefantrine and decrease the exposure of artemether and its active metabolite dihydroartemisinin when co-administered as artemether-lumefantrine. Co-administration of artemether-lumefantrine with ritonavir-boosted lopinavir (LPV/r) significantly reduces artemether C_{max} and AUC but significantly increases lumefantrine exposure. Co-administration of etravirine reduced the AUC of artemether (38%), dihydroartemisinin (15%), and lumefantrine (13%) at steady state. Co-administration of etravirine with artemether-lumefantrine may lower the antimalarial activity of artemether and should therefore be used with caution. Co-administration of artemether-lumefantrine with efavirenz or nevirapine results in a reduction in artemether, dihydroartemisinin, lumefantrine, and nevirapine exposure. Co-administration of darunavir/ritonavir reduced the AUC of artemether (16%) and dihydroartemisinin (18%) but increased the AUC of lumefantrine (28%) at steady state. Darunavir/ritonavir can be co-administered with artemether-lumefantrine without dose adjustment but should be used with caution. Co-administration of artemether-lumefantrine has no effect on etravirine, darunavir, or ritonavir AUC. No drug-related serious adverse events are reported during the studies. There has been limited information on the interaction between other ACTs and protease inhibitors. Co-administration of artesunate-mefloquine with ritonavir decreases dihydroartemisinin exposure. Co-administration of artesunate-pyronaridine with ritonavir increases ritonavir exposure. In the presence of ritonavir-boosted lopinavir (LPV/r), artesunate Cmax and systemic exposure (AUC) are significantly increased (45–80%), while the metabolic ratio of dihydroartemisinin to artesunate is significantly reduced (72%). On the other hand, mefloquine C_{max} and systemic exposure are significantly reduced (19–37%). Lopinavir C_{max} is significantly reduced (22%) but without significant change in AUC. Drug treatments are generally well tolerated with no serious adverse events. The reduction in systemic exposure of all investigated drugs raises concerns of an increased risk of treatment failure rate in coinfected patients and should be further investigated.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) tend to decrease the exposures of artemether, dihydroartemisinin, and lumefantrine when co-administered with artemether-lumefantrine. However, the exposure of nevirapine is increased. Co-administration of artesunate-mefloquine with nevirapine increases artesunate exposure.

Other Currently Used Antimalarial Drugs

Tetracycline and Derivatives

Tetracyclines are synthetic antibiotics derived from a cycline naturally produced by *Streptomyces* bacteria. Doxycycline is a long-acting derivative. Tetracyclines are generally used in the treatment of infections of the respiratory tract and the intestines and are also used in the treatment of chlamydia. Their most common current use is in the treatment of moderately severe acne and rosacea. Doxycycline is also used as a prophylactic treatment for infection by *Bacillus anthracis* (anthrax) and is effective against *Yersinia pestis*, the infectious agent of bubonic plague. Tetracyclines remain the treatment of choice for infections caused by chlamydia (trachoma, psittacosis, salpingitis, urethritis, and *L. venereum* infection), Rickettsia (typhus, Rocky Mountain spotted fever), brucellosis, and spirochetal infections (borreliosis, syphilis, and Lyme disease). In addition, they may be used to treat anthrax, plague, tularemia, and Legionnaires' disease. They may have a role in reducing the duration and severity of cholera, although drug resistance is mounting and their effect on overall mortality is questioned. Tetracycline derivatives



Pharmacology of Antimalarial Drugs, Current Anti-malarials, Fig. 9 Chemical structures of tetracycline and doxycycline

are currently being investigated for the treatment of certain inflammatory disorders.

Tetracycline and doxycycline (Fig. 9a and b) are used for malaria treatment and prophylaxis, as well as treating certain forms of human filariasis. Both have molecular weight of 444.4.

Antimalarial Activities and Therapeutic Indications for Malaria

Tetracycline and doxycycline are broad-spectrum antibiotics which are inhibitors of protein synthetase by disrupting messenger RNA and transfer RNA. Both are consistently active against all species of malaria. Tetracycline and doxycycline are slow-acting blood schizontocidal agents. Currently, doxycycline is used in combination with quinine or artesunate for treatment of chloroquine-resistant and multidrug-resistant *P. falciparum.* Doxycycline remains effective in combination with quinine or artesunate at a dose of 200 mg for 7 days. In addition, it is also indicated for the prophylaxis of malaria at a dose of 100 mg/day starting at the day of arrival in endemic areas and continuing for up to 4 weeks after returning.

Adverse Drug Reactions and Toxicity

Common adverse drug reactions of doxycycline include gastrointestinal disturbance (nausea, vomiting, and diarrhea), particularly with higher doses. Oral doxycycline should be administered with food to reduce gastric irritation. Other reactions that can occasionally occur are dry mouth, glossitis, stomatitis, dysphagia, and esophageal ulceration. Esophageal irritation can be reduced by administration of doxycycline with a full glass of water. Doxycycline crosses the placenta and may cause discoloration of teeth and possible bone growth retardation in the fetus and in young infants. They also discolor teeth and cause enamel hypoplasia in young children. However, doxycycline has recently been recommended by the American Association of Pediatrics to be used safely in children of all ages if given less than 28 days. Hypersensitivity reactions such as urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, and exacerbation of systemic lupus erythematosus may occur. Rare severe adverse reactions that can be found include benign intracranial hypertension in adults and hematological abnormalities such as hemolytic anemia, thrombocytopenia, neutropenia, eosinophilia, and thrombophlebitis (with prolonged intravenous administration). Expired tetracyclines or tetracyclines allowed to stand at a pH less than 2 are reported to be nephrotoxic due to the formation of a degradation product, anhydro-4-epitetracycline causing Fanconi syndrome.

Contraindications

Doxycycline is contraindicated in patients with known hypersensitivity to tetracyclines and related compounds. Doxycycline is categorized by the FDA as a class D drug in pregnancy. Fatal necrosis has been reported with doxycycline use in pregnancy.

As with all tetracyclines, it is contraindicated in pregnancy through infancy, due to the potential for disrupting bone and tooth development. The exception is in the treatment of anthrax or where other medications are contraindicated or ineffective.

Caution

Doxycycline should be used with caution in patients with gastric or intestinal diseases such as colitis, who may be at greater risk for pseudomembranous colitis. In addition, the use of doxycycline in patients with established systemic lupus

erythematosus should be with caution as the drug may worsen the clinical conditions.

Pharmacokinetics

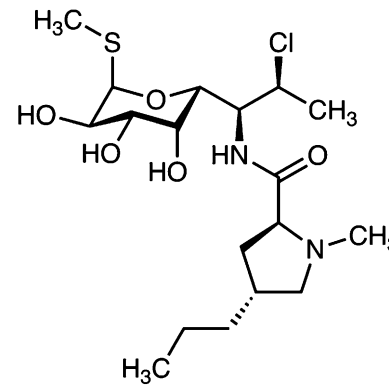
Pharmacokinetic parameters of doxycycline following dose regimens recommended for treatment and prophylaxis of malaria are summarized in Table 1.

There is a marked interindividual variability in doxycycline pharmacokinetics, depending on age and the co-administered drugs. Doxycycline is highly lipophilic and is rapidly and almost completely absorbed after oral administration with bioavailability approaching 100%. Unlike tetracycline, absorption of doxycycline is not markedly changed in the presence of food. However, the rate and extent of absorption of doxycycline are markedly reduced when taken with milk or other dairy products. Doxycycline should not therefore be administered with these products.

Doxycycline is widely distributed in body fluids and tissues including the bone marrow, breast milk, livers, kidneys, gastrointestinal tract, and spleen. Penetration into sputum is 8–28% over 16 h. Penetration into saliva is poor, while biliary concentration exceeds serum by manyfold. The drug also crosses the placenta. Approximately 80–95% of doxycycline binds to plasma proteins. The drug is metabolized in the liver by an unknown mechanism. No metabolites have been identified to date. Tetracyclines including doxycycline undergo enterohepatic recirculation, resulting in slow clearance. Doxycycline is eliminated unchanged by both the renal and biliary routes. Bile concentrations may be 10–25 times those in plasma/serum. Approximately 35–60% is excreted in urine and the remainder in feces. The $t_{1/2}$ of doxycycline is not affected by impaired renal function, renal failure, or hemodialysis. Therefore, dose adjustment is not required for these patients.

Factors Associated with Altered Drug Exposure and/or Treatment Response

Doxycycline absorption is decreased in the presence of antacids, bismuth subsalicylate, proton-pump inhibitors, and oral iron preparations. Hepatic inducers such as rifampicin, anticonvulsants (carbamazepine, phenytoin, phenobarbital), and chronic alcohol use may accelerate doxycycline metabolism resulting in increased drug exposure (AUC) and C_{max}. The $t_{1/2}$ is also shortened.



Pharmacology of Antimalarial Drugs, Current Antimalarials, Fig. 10 Chemical structure of clindamycin

Clindamycin

Antimalarial Activities and Therapeutic Indications for Malaria

Clindamycin (Fig. 10) is a semisynthetic derivative of lincomycin, a natural antibiotic produced by the actinobacterium *Streptomyces lincolnensis*. It is obtained by 7(*S*)-chloro-substitution of the 7(*R*)-hydroxyl group of lincomycin.

Clindamycin is used as antibacterial drug, primarily Gram positive and anaerobic infections caused by susceptible anaerobic bacteria, including dental infections and infections of the respiratory tract, skin, and soft tissue, peritonitis, and bone and joint infections. Topical application of clindamycin phosphate is used to treat mild-to-moderate acne.

For treatment of malaria, clindamycin is always used in combination with standard blood schizontocidal drugs particularly quinine and artesunate for treatment of uncomplicated and severe malaria. It is the first-line treatment in first-trimester pregnancies. Clindamycin should not be used alone as an antimalarial drug due to its slow action.

Its mechanism of action involves inhibition of microbial protein synthesis by preferential binding to the 50S ribosomal subunit and inferences with peptide chain initiation. It is active on apicoplast and leads to delayed cell death.

Adverse Reactions and Toxicity

Clindamycin is generally well tolerated after oral administration. Adverse reactions include nausea, vomiting, abdominal pain or cramps, rash, or pruritus. High dose (both intravenous and oral) of clindamycin may cause a metallic taste in the mouth. Rarely, clindamycin therapy has been associated with anaphylaxis, blood dyscrasia (leukopenia, agranulocytosis, eosinophilia, and thrombocytopenia), erythema multiforme, polyarthritis, jaundice, raised liver enzymes, hepatotoxicity, and renal dysfunction. Some parenteral formulations contain benzyl alcohol, which may cause fatal "gasping syndrome" in neonates.

Contraindications

Clindamycin is contraindicated in patients with known hypersensitivity to clindamycin and structurally related compounds.

Caution

Clindamycin should be used with caution in patients with gastrointestinal diseases (increased risk of pseudomembranous colitis) and severely ill elderly patients (increased risk of diarrhea). Close monitoring of adverse reactions is required when clindamycin is administered to neonates (risk of toxic plasma drug concentrations). Dose optimization may be required when clindamycin is given to patients with moderate-to-severe liver disease due to impairment of drug clearance. Patients with HIV infection should be closely monitored if clindamycin is to be given due to possibility of increased plasma drug exposure to toxic level.

Pharmacokinetics

Pharmacokinetic parameters of clindamycin are summarized in Table 1.

Clindamycin is rapidly absorbed after oral administration, with an oral bioavailability of approximately 90%. About 90% is bound to plasma proteins and accumulates in leukocytes, macrophages, and bile. It is widely distributed throughout the body fluids and tissues, including the bone, but significant levels are reached in CSF.

Clindamycin is metabolized in the liver by CYP3A4 into the active *N*-demethyl and sulfoxide metabolites and some inactive metabolites. About 10% of a dose is excreted in the urine as active drug or metabolites and about 4% in feces. The remainder is excreted as inactive metabolites. Excretion is slow and takes place over several days. The drug is not effectively removed from the body by dialysis.

Clindamycin $t_{1/2}$ may be prolonged and CL reduced in neonates and patients with renal impairment. However, dose modification is not considered necessary.

There has been no data published on the pharmacokinetics of clindamycin in pregnant women, although it is used to treat malaria in pregnancy.

Factors Associated with Altered Drug Exposure and/or Treatment Response

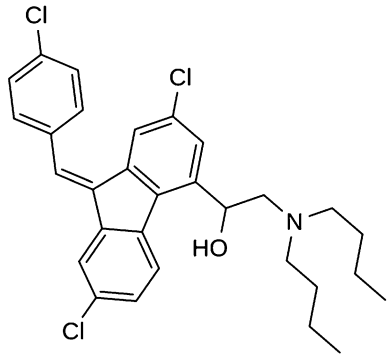
Clindamycin absorption is delayed with aluminum salts and kaolin. It is a weak-to-moderate inhibitor of CYP3A in vitro, and therefore potential for drug-drug interactions involving clindamycin is low. Nevertheless, the use in patients HIV infection should be with caution. Systemic drug exposure and plasma protein binding of clindamycin have been shown to be increased, while CL/F and Vd/F reduced in HIV-infected patients.

Clindamycin prolongs effects of neuromuscular blocking agents and may lead to respiratory depression. Possible antagonism and cross-resistance may occur with macrolides and chloramphenicol. Clindamycin antagonizes parasympathomimetics such as neostigmine.

Lumefantrine

Antimalarial Activities and Therapeutic Indications for Malaria

Lumefantrine (benflumetol: Fig. 11) is a fluorine derivative belonging to the arylamino alcohol group of antimalarials structurally related to quinine, mefloquine, and halofantrine. Mechanism of



Pharmacology of Antimalarial Drugs, Current Anti-malarials, Fig. 11 Chemical structure of lumefantrine

action is thought to be similar to the others in the group by preventing heme detoxification within the parasite food vacuole, thus causing accumulation of the toxic heme complex. It is effective against multidrug-resistant *P. falciparum* malaria. Combination of lumefantrine and artemether (ACT) has proved to be effective in treating uncomplicated acute falciparum malaria. The drug is not available as a single drug and has not been used as monotherapy, which should slow the selection and spread of resistance to this drug.

Pharmacokinetics

Pharmacokinetic parameters of lumefantrine as a component of artemether-lumefantrine combination (ACT) following dose regimen recommended for treatment and prophylaxis of malaria are summarized in Table 1.

Oral absorption of lumefantrine is increased when co-administered with fatty foods or milk due to its highly lipophilic nature. This may lead to a marked variation in drug absorption among individuals. Its bioavailability and t_{max} vary within and between individuals, primarily due to fat-dependent absorption. Furthermore, there is a nonlinear absorption of lumefantrine which is saturated at the currently recommended doses. Plasma protein binding is high (99.7%). Lumefantrine is extensively metabolized in the liver, primarily by the CYP3A4, to the active metabolite desbutyllumefantrine. $T_{1/2}$ is about 3 days.

Factors Associated with Altered Drug Exposure and/or Treatment Response

Plasma lumefantrine concentrations achieved in children aged lower than 5 years are significantly lower than in older children and adults. This has been reported to be associated with increased risks of recrudescence and earlier reinfections. Lumefantrine disposition is also altered in women in the second and third trimesters of pregnancy. Due to a significant increase in Vd/F, systemic drug exposure is markedly lower. The lower day 7 concentrations reported could be an important factor in clinical failure.

Lumefantrine and amodiaquine are metabolized by CYP3A4 and CYP2C8, respectively, and plasma concentration may be theoretically decreased by the inducers of these enzymes including rifampicin.

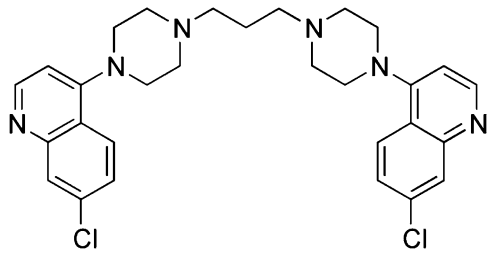
Piperaquine

Antimalarial Activities and Therapeutic Indications for Malaria

Piperaquine (Fig. 12) is a bisquinoline antimalarial drug structurally related to chloroquine and other 4-aminoquinolines. The drug was synthesized independently in France and China in the 1960s. Piperaquine replaced chloroquine for malaria prophylaxis in China in 1978. Nevertheless, with the emergence of *P. falciparum* piperaquine-resistant strains, piperaquine use was decreased in the late 1980s. In the 1990s, piperaquine was reconsidered as one of the components of short-course ACTs in combination with dihydroartemisinin, trimethoprim, and primaquine (China-Vietnam 4 or CV4 and China-Vietnam 8 or CV8).

Piperaquine has a very long $t_{1/2}$ of about 2–3 weeks and consequently could be expected to provide a long period of posttreatment prophylaxis.

Both the mechanisms of action and of resistance of piperaquine have not been well characterized but are likely to be similar to chloroquine. Mutation of *pfcrt* (*P. falciparum* chloroquine-resistant transporter) as well as increase in plasmepsin II/III copy number has been implicated in piperaquine-resistant *P. falciparum*. Cross-resistance between piperaquine and chloroquine has been reported.



Pharmacology of Antimalarial Drugs, Current Anti-malarials, Fig. 12 Chemical structure of piperaquine

However, piperaquine has also been shown to be active against highly chloroquine-resistant *P. falciparum.* Resistance to both artemisinin and piperaquine is now prevalent in Cambodia, as demonstrated by the increase in the number of cases of dihydroartemisinin-piperaquine treatment failure.

Adverse Reactions and Toxicity

The symptomatic adverse reactions produced by piperaquine are more or less tolerable. These include dizziness, headache, nausea, vomiting, anorexia, myalgia, cough, asthenia, arthralgia, abdominal distress, pyrexia, eosinophilia, and QTc prolongation.

Pharmacokinetics

Piperaquine pharmacokinetic properties are similar to those of chloroquine. The kinetics of piperaquine in adult patients is described by a three-compartment model with first-order elimination and two first-order absorption processes. Piperaquine is highly lipid soluble, and its oral bioavailability may be lower when given without any food. A large quantity of co-administered fat enhances absorption significantly.

Piperaquine is highly bound to plasma proteins (>98%), with a very large Vd/F (>100 l/kg), a low CL/F (1–2 l/h/kg), and a consequently long $t_{1/2}$ (13–28 days).

Factors Associated with Altered Drug Exposure and/or Treatment Response

The pharmacokinetic properties of piperaquine are affected by body weight and age. Concentrations of piperaquine, when co-administered with dihydroartemisinin, are lower at the beginning of the terminal elimination phase in children than in adults. This low plasma piperaquine concentration on day 7 has been shown to be associated with treatment failure. There are no clinically important differences in the pharmacokinetics of dihydroartemisinin or piperaquine between pregnant and nonpregnant women.

Plasma concentration of piperaquine and potential toxicity are increased when piperaquine is given with verapamil, indinavir, lopinavir/ritonavir, HMG-CoA reductase inhibitors (statins), and cyclosporine. Co-administration of piperaquine with barbiturates, chronic alcohol use, rifampicin, efavirenz, nevirapine, phenytoin, or carbamazepine increases metabolism of piperaquine and therefore reduces plasma concentration of piperaquine with reduced effectiveness.

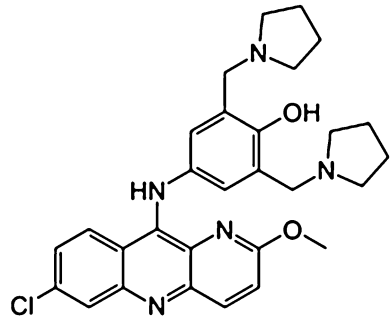
Co-administration with drugs that prolong QTc interval increases piperaquine risk of cardiotoxicity.

Pyronaridine

Antimalarial Activities and Therapeutic Indications for Malaria

Pyronaridine is (Fig. 13), a Mannich base 1-aza-acridine structurally related to mepacrine. It is a benzonaphthyridine derivative which was first synthesized in 1970 at the Institute of Chinese Parasitic Disease, Chinese Academy of Preventive Medicine. It was used in China for the treatment of malaria as a single agent for the past 30 years. Pyronaridine-artesunate has been developed by the Medicines for Malaria Venture (MMV) and Shin Poong Pharm Co Ltd (Republic of Korea) for the treatment of acute uncomplicated *P. falciparum* and blood stage *P. vivax* malaria with a fixed-dose combination tablet and granule formulation for pediatric administration (as a potential ACT). It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.

Pyronaridine exhibits high efficacy, including against chloroquine- and amodiaquine-resistant strains, and the reassurance of many years of successful use in China as monotherapy and in combination with other antimalarials, without the



Pharmacology of Antimalarial Drugs, Current Anti-malarials, Fig. 13 Chemical structure of pyronaridine

development of widespread drug resistance. Pyronaridine has potent in vitro activity against *P. falciparum* strains and clinical isolates including those that are resistant to other antimalarials. In vivo animal models indicate a synergistic effect between pyronaridine and artemisinins against parasites resistant to one or both components, restoring efficacy against these strains. Consequently, pyronaridine represents an ideal candidate for combination therapy with artemisinin derivatives, such as artesunate.

Almost all published clinical trials to date used the Chinese enteric-coated tablet formulation with 175 mg of the tetraphosphate, equal to 100 mg base, with dosages lipophilic at pH 7.4 (logD 0.34); lipophilicity was reduced at pH 5. The base is more liposoluble than the salt. Clinical studies of the combination of pyronaridine tetraphosphate and artesunate are encouraging and show it to be a promising new artemisinin combination therapy for the treatment of both *P. falciparum* and *P. vivax* malaria in adult, children, and infant populations. The drug is administered as pyronaridine tetraphosphate (56.89% base), a yellow, odorless powder with a bitter taste.

The mechanism(s) by which pyronaridine acts as an antimalarial appears to be similar to chloroquine through inhibition of the production of, and formation of complexes with, β-hematin to enhance hematin-induced human blood cell lysis. Pyronaridine also inhibits glutathione-dependent heme degradation. The mechanism by which resistance to pyronaridine develops is unknown but may be due to a direct effect on the pyronaridine mechanism of action.

Adverse Reactions and Toxicity

Pyronaridine also appears to be well tolerated in clinical studies. Overall, the acute and subacute toxicity of pyronaridine is generally less than that of chloroquine in all animal species tested. Adverse reactions are mild and are usually resolved within 2 days of starting therapy. The most common adverse events after oral pyronaridine therapy in many cases are similar to the symptoms of malaria, i.e., dizziness, nausea, vomiting, and abdominal discomfort. The incidence of cardiovascular toxicity is also less than that of chloroquine. There are no unexpected findings that would be a particular cause for concern at therapeutic levels in human subjects. The concern of liver toxicity which led to a restriction of pyronaridine use has now been resolved. However, evidence of embryotoxicity in rodents suggests that pyronaridine should be used with caution during pregnancy. There are also some reports of palpitations and allergic skin reaction. Similarly to chloroquine, pruritus may also rarely occur in African patients.

Pharmacokinetics

Oral bioavailability of pyronaridine is relatively low. The relative bioavailability of enteric-coated tablets and capsules are about 20% and 32%, respectively. In vitro studies using human CYP450 isoforms indicated that pyronaridine could be metabolized by CYP1A2, CYP2D6, and CYP3A4. Quinoneimine metabolites of aminoquinolines are thought to cause the toxicity problems. Pyronaridine preferentially associates with blood cells with a blood/plasma distribution of 1.2–1.7 in human. Plasma protein binding is high (92–96%). As pyronaridine concentrates in erythrocytes, plasma assays may underestimate pyronaridine concentrations. The drug is extensively distributed to various body tissues. The $t_{1/2}$ of pyronaridine in healthy adult subjects and adult malaria subjects are estimated to be 11.3 and 13.2 days, respectively. The pharmacokinetics of pyronaridine appears to be altered in patients with

malaria. In children, the $t_{1/2}$ appears to be shorter than adults ranging from 6.6 to 9.0 days.

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