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Chapter 1
Introduction

Malaria is a major tropical health burden worldwide and currently the most important parasitic disease in humans (White et al. 2014). It is prevalent in 108 countries that are inhabited by approximately 3 billion people. The most recent estimates from the World Health Organization (WHO) (WHO 2014a) suggest there were approximately 207 million cases of malaria in 2012 and 627,000 deaths related to the disease. Most deaths occurred among children living in Africa. However, since 2000, deaths due to malaria have decreased by 42 % worldwide and rates of malaria-related deaths among children in Africa have decreased by 54 % (WHO 2014a).

The four most common causes of malaria in humans are *Plasmodium falciparum, P. vivax, P. malaria,* and *P. ovale*. *P. falciparum* is the most fatal and represents the most common infection in Africa (Baird 2005). *P. falciparum* and *P. vivax* have approximately equal prevalence in Asia, and South and Central America (White et al. 2014). Transmission in these regions is typically much lower than in Africa and follows seasonal trends. In areas where transmission is high and persistent year around, acquired immunity can develop especially in adults. Unfortunately, children rarely acquire immunity and this is a contributor to the morbidity and mortality seen in this population.

The female *Anopheles* mosquito is responsible for the transmission of the *Plasmodium* parasites that cause clinical disease. The intensity of transmission is determined by the mosquito density, longevity, biting habits, and efficiency (White et al. 2014). Considering these factors, approximately 25 of over 400 anopheline species are good vectors for spread of infection. The *Anopheles gambiae* complex, which is present in Africa, not only satisfies these factors but is also robust to environmental change, breeds readily, and preferentially bites humans. These vector considerations highlight some of the current challenges relating to malaria spread and control.

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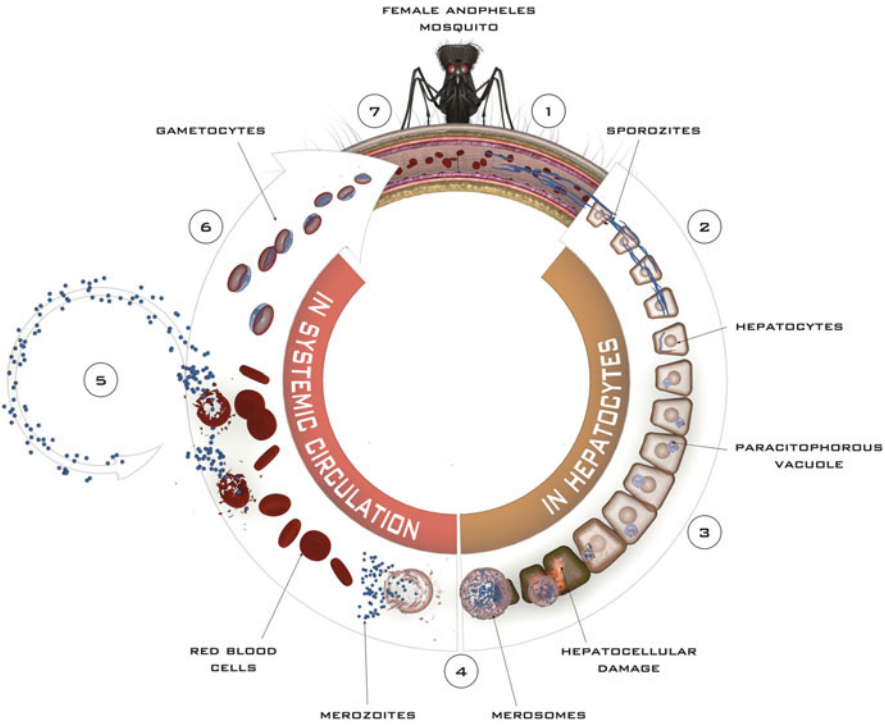

Fig. 1.1 *Plasmodium falciparum* Lifecycle (Wilby et al. 2012). The lifecycle of *Plasmodium falciparum* in the human host. (1) Sporozoites are introduced from an infected *Anopheles* mosquito, while taking a blood meal; (2) Sporozoites migrate to the hepatic circulation and infiltrate neighboring hepatocytes; (3) Sporozoites undergo development and differentiation in the hepatocytes, producing thousand of merozoites; (4) Merozoites are liberated from the hepatocyte in small cellular vesicles called merosomes, which disintegrate in the systemic circulation releasing the merozoites; (5) Merozoites invade erythrocytes and continue maturation and division to become schizonts; the red blood cell ruptures resulting in the systemic release of more merozoites, that infect more erythrocytes; (6) Some merozoites differentiate into male and female gametocytes; (7) Gametocytes are then consumed by uninfected female *Anopheles* mosquito during a blood meal; cycle is then repeated (Reproduced with permission from: Ann Pharmacother 2012; 46 (3):384–93)

The *P. falciparum* lifecycle (Fig. 1.1) consists of two stages: asymptomatic hepatic (pre-erythrocytic) followed by symptomatic blood (erythrocytic) stage (Casares et al. 2010). During the erythrocytic phase, patients commonly present with fever, chills, weakness, headache, nausea, vomiting, and diarrhea. While erythrocyte stages are most responsible for these observable clinical symptoms, damage to hepatocytes and hepatomegaly may occur due to hepatic invasion during pre-erythrocyte phases (Sowunmi 1996).

1.1 Clinical Presentation

Initial malaria symptoms are typically nonspecific in nature, which makes it challenging to differentiate from a systemic viral illness or vice versa. Symptoms typically consist of headache, fatigue, abdominal discomfort, and muscle and joint aches. These symptoms are commonly followed by fever, chills, perspiration, and anorexia (WHO 2010). If malaria is not recognized and treated promptly (especially for *P. falciparum*), severe malaria can develop which usually presents with at least one of the following: coma, metabolic acidosis, severe anemia, hypoglycemia, acute renal failure, or pulmonary edema (WHO 2010). The severity of symptoms depends on both the time before receiving effective treatment and degree of protective immunity acquired in the host. For example, adults and adolescents living in endemic areas will not always suffer from clinical disease, due to their acquired immunity and harboring of low-level parasite burdens.

1.2 Diagnosis

Accurate diagnosis is required for effective treatment and control of malaria. It is very important that diagnostic tests of high quality are available throughout endemic regions, due to the significant morbidity and mortality associated with the disease as well as considerable over-diagnosis resulting from the non-specific nature of presentation (WHO 2010). Furthermore, accurate diagnosis should be completed in a timely manner (rapidly, where applicable), in order to ensure proper care is given (WHO 2010).

The clinical decision-making process first begins when the patient presents with signs and/or symptoms. As discussed, typical malarial signs include elevated temperature and symptoms and are generally non-specific but include weakness, fatigue, headache, nausea, vomiting, diarrhea, or general malaise (WHO 2010). Severity of symptoms may vary greatly between individuals. Due to the non-specific nature of presenting complaints, it is not advised to base treatment decisions on clinical presentation alone without identification of malaria parasites in the blood (WHO 2014b).

Two forms of diagnostic testing are generally recommended (WHO 2010). Both require parasitological confirmation by either microscopy or a rapid diagnostic test (RDT) (WHO 2014b). Thick and thin blood film microscopy is typically considered the gold standard test for diagnosis. Identification of malaria parasites and determination of parasite burden help clinicians make treatment decisions. RDTs are available that work by detecting PfHRP2, pan-malaria or species-specific lactate dehydrogenase, or aldolase antigens in capillary blood. While RDTs offer a quick and efficient alternative to microscopy testing, some concerns still exist regarding species

identification and overall sensitivity. Other limitations include price and the inability to quantify parasitemia (White et al. 2014). The WHO has published guidelines for evaluation of these tests, including considerations for field-based studies and testing (Bell and Peeling 2006).

1.3 Treatment Recommendations

Once a firm diagnosis is established, prompt treatment using recommended antimalarial combinations is warranted. The WHO released the second edition of their guidelines for the treatment of malaria in 2010 (WHO 2010). The guidelines summarize treatment for all types of malaria and special populations. Recommended treatment regimens are given in Table 1.1. Briefly, artemisinin-based combination therapy (ACT) is the current gold standard treatment for most malaria subtypes and affected populations. Regimens consist of an artemisinin derivative paired with at least one antimalarial from a different class. ACT is especially important for *P. falciparum*, due to high levels of resistance to chloroquine in most endemic areas. However, chloroquine-based regimens can still be considered to treat other malaria subtypes.

There are special populations that require additional treatment considerations. The recommendations for treatment of pregnant women with uncomplicated *P. falciparum* are summarized in Table 1.1 (WHO 2010). Although artemisinin derivatives have not been associated with toxicity, greater experience with quinine makes this agent first line (in combination with clindamycin) for women in their first trimester of pregnancy. However, more data are available for ACTs in second and third trimesters that show these agents are well tolerated and free from any known major adverse effects. It should also be noted that lactating women could receive standard antimalarial treatment, except for dapsone, primaquine, and tetracyclines. ACTs are still first line for infants and young children but care should be given to ensure adequate dosing as drug concentrations may be altered in these patients. Two special considerations exist for HIV patients with malaria. First, treatment or prevention with sulfadoxine-pyrimethamine should not be given to those patients receiving cotrimoxazole (due to similar mechanisms of action and synergistic adverse reactions). Additionally, amodiaquine should be avoided in patients taking zidovudine or efavirenz antiretroviral therapy due to hepatotoxicity. Finally, travelers returning to non-endemic countries can be treated with one of the following: atovaquone plus proguanil, artemether plus lumefantrine, dihydroartemisinin plus piperaquine, quinine plus doxycycline or clindamycin (WHO 2010).

Table 1.1 Recommended regimens for treatment of malaria (WHO 2010)

Category	Recommended agents	Sample treatment regimen	Notes
Uncomplicated *P. falciparum* malaria	Artemether plus lumefantrine	FDC: Artemether 20 mg, lumefantrine 120 mg 5–14 kg—1 tablet 15–24 kg—2 tablets 25–34 kg—3 tablets >34 kg—4 tablets Given orally twice daily for 3 days	Lumefantrine absorption enhanced by co-administration of fat
	Artesunate plus amodiaquine	Target dose of 4 mg/kg/day artesunate and 10 mg/kg/day amodiaquine given orally once daily for 3 days	
	Artesunate plus mefloquine	Target dose of 4 mg/kg/day artesunate given orally once daily for 3 days. Mefloquine 25 mg/kg (split over 2 days as 15 mg/kg and 10 mg/kg or over 3 days as 8.3 mg/kg once daily for 3 days)	
	Artesunate plus sulfadoxine-pyrimethamine	Target oral dose of 4 mg/kg/day artesunate given once daily for 3 days plus SP 25/1.25 mg/kg as a single dose on day 1	
	Dihydroartemisinin plus piperaquine	Target oral dose of 4 mg/kg/day DHA plus 18 mg/kg/day piperaquine once daily for 3 days	
Uncomplicated *P. falciparum* malaria in pregnant women (first trimester)	Quinine plus clindamycin	7 days	Artesunate plus clindamycin indicated if this treatment fails
	ACT (as above)		If only treatment immediately available, or if failure documented with quinine/clindamycin, or if patients at risk of non-compliance with 7 days regimen

(continued)

Table 1.1 (continued)

Category	Recommended agents	Sample treatment regimen	Notes
Uncomplicated *P. falciparum* malaria in pregnant women (second and third trimesters)	ACT known to be effective in the country/region or artesunate plus clindamycin for 7 days or quinine plus clindamycin for 7 days	As above	ACTs not been found to be associated with maternal or fetal risks
Severe *P. falciparum* malaria	Artesunate	2.4 mg/kg body weight IV or IM given at 0, 12, and 24 h, then daily	Parenteral antimalarials given for minimum 24 h and then can complete treatment with ACT above
	Artemether (if artesunate not available)	3.2 mg/kg body weight IM given at 0 h, then 1.6 mg/kg per day	Parenteral antimalarials given for minimum 24 h and then can complete treatment with ACT above
	Quinine (if artesunate not available)	20 mg salt/kg body weight on at 0 h (IV infusion or divided IM injection), then 10 mg/kg body weight every 8 h (infusion rate should not exceed 5 mg salt/kg/h)	Parenteral antimalarials given for minimum 24 h and then can complete treatment with ACT above
Uncomplicated *P. vivax* malaria	Chloroquine plus primaquine	Chloroquine 25 mg base/kg body weight divided over 3 days plus primaquine 0.25 mg base/kg body weight with food once daily for 14 days.	In Oceania and South-East Asia, primaquine dose should be 0.5 mg/kg. In patients with mild to moderate G6PD deficiency, primaquine 0.75 mg base/kg body weight given once weekly for 8 weeks. Primaquine contraindicated in severe G6PD deficiency
	ACTs combined with primaquine for chloroquine-resistant vivax		Artesunate plus sulfadoxine-pyrimethamine not effective in many places

(continued)

Table 1.1 (continued)

Category	Recommended agents	Sample treatment regimen	Notes
Malaria caused by *P. ovale* and *P. malariae*	As above for *P. vivax* treatment with the exception that *P. malarae* does not require addition of primaquine		

ACT artemisinin-based combination therapy, *DHA d*ihydroartemisinin, *FDC* fixed dose combination, *G6PD* glucose-6-phosphate dehydrogenase, *IM* intramuscular, *IV* intravenous, *SP* sulfadoxine-pyrimethamine

1.4 Prophylaxis

Chemoprophylaxis for malaria is recommended for travelers visiting endemic regions (CDC 2011). While each individual should determine country-specific drug sensitivities prior to choosing an antimalarial, the following agents are generally recommended for chemoprophylaxis: atovaquone/proguanil, doxycycline, mefloquine, chloroquine, and primaquine. Dosing of the listed regimens ranges from daily (atovaquone/proguanil, doxycycline, primaquine) to weekly (mefloquine, chloroquine). Chemoprophylaxis should be used in combination with non-pharmacological prevention measures (insect repellant, insecticide-treated bed net, long-sleeved shirts and long pants) in order to increase effectiveness and prevent infection.

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Chapter 2
Pharmacology of Recommended Antimalarial Agents

Currently recommended antimalarial agents consist of a variety of agents from different drug classes. Differences in mechanisms of action allow for synergistic combinations and increased therapeutic success. A summary of pharmacological and pharmacokinetic considerations is given in Table 2.1 for chloroquine, amodiaquine, sulfadoxine, pyrimethamine, mefloquine, quinine/quinidine, artemisinin (the artemisinin agents, artemether, artesunate, and dihydroartemisin, are closely related and summarized as a class, where applicable), lumefantrine, primaquine, atovaquone, and proguanil.

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Table 2.1 Pharmacology of recommended antimalarials (Brunton et al. 2010; Lexi Comp 2013; Sanofi-Aventis 2010)

Drug	General chemistry	Mechanism of action	Clinical pharmacology	Clinical pharmacodynamics
Chloroquine	4-aminoquinoline	Interferes with heme detoxification. Concentrates in digestive vacuoles and binds to heme and disrupts its sequestration. Parasite killed by resulting oxidative damage to membranes, digestive proteases, or other biomolecules. Binds to and inhibits DNA and RNA polymerase	**Absorption**: well absorbed from gastrointestinal tract and tissues **Distribution**: extensively sequesters in tissues (liver, spleen, kidney, lung, melanin-containing tissues). 60 % bound to plasma proteins **Metabolism**: metabolized to desethylchloroquine and bidesethylchloroquine **Elimination**: unchanged chloroquine and desethylchloroquine account for >50 % and 25 % of urinary products. Elimination t1/2 = 3–5 days. Terminal t1/2 = 30–60 days	Mostly effective against erythrocytic forms of *P. vivax, ovale, and malariae*. Mostly now resistant to *P. falciparum* in endemic regions but maintains activity against some strains. Resistance conferred by *pfcrt* (*P. falciparum* chloroquine resistance transporter). Alleles with 4–8 mutations highly associated with resistance by encoding putative transporter that actively effluxes chloroquine away from heme target. Variant *pfcrt* alleles may partially confer resistance to other agents (amodiaquine, quinine) but increase susceptibility to lumefantrine and artemisinin derivatives
Amodiaquine	Synthetic 4-aminoquinolone	Not entirely known. Considered to penetrate red blood cells and prevent parasite from polymerizing heme into hemozoin, leading to parasite death	**Absorption**: well absorbed from gastrointestinal tract **Distribution**: volume of distribution 20–40 L/kg **Metabolism**: high first pass metabolism via CYP2C8 to monodesethylamodiaquine. Further presumed to undergo oxidation and glucuronidation	Given in combination with artesunate for *P. falciparum*. Resistance documented to amodiaquine for *P. falciparum* but activity remains against some chloroquine-resistant strains

			Elimination: 2 % excreted unchanged in urine. Terminal t1/2 = 9–18 days	
Sulfadoxine	Sulfonamide	Interferes with folic acid synthesis via competitive inhibition of dihydropteroate synthase	**Absorption:** slow but completely absorbed (Tmax = 4 h) **Distribution**: apparent volume of distribution = 0.14 L/kg, 90 % plasma protein bound **Metabolism**: 5 % appears in plasma as acetylated metabolite, 2–3 % as glucuronide **Elimination**: primarily eliminated via kidneys	Synergy with pyrimethamine results from inhibition of: (1) utilization of p-aminobenzoic acid for synthesis of dihydropteroic acid and (2) reduction of dihydrofolate to tetrahydrofolate. Resistance conferred by several point mutations in dihydropteroate synthase gene. Resistance to both sulfadoxine and pyrimethamine causing decline in use
Pyrimethamine	2,4-diaminopyrimidine	Inhibits dihydrofolate reductase, resulting in inhibition of tetrahydrofolic acid synthesis	**Absorption**: well absorbed from gastrointestinal tract **Distribution**: extensively distributes into tissues, 80–87 % plasma protein bound **Metabolism**: hepatic metabolism to several metabolites **Elimination**: 20–30 % excreted as unchanged drug in urine. Elimination t1/2 = 80–95 h	Slow-acting blood schizontocide. Efficacy against hepatic forms of *P. falciparum* less than proguanil. Fails to eradicate *P. vivax* hypnozoites or gametocytes of any species. Resistance conferred by mutations of dihydrofolate reductase. Resistance to both sulfadoxine and pyrimethamine causing decline in use. Recommended for intermittent preventative treatment of malaria in pregnancy
Mefloquine	4-quinoline	Shown to associate with intra-erythrocytic hemozoin (similar mechanism of action as	**Absorption**: rapidly absorbed but high interindividual variability (enterogastric and enterohepatic circulation)	Highly effective blood schizonticide with no activity against hepatic stages or mature gametocytes of *P. falciparum.*

(continued)

Table 2.1 (continued)

Drug	General chemistry	Mechanism of action	Clinical pharmacology	Clinical pharmacodynamics
		chloroquine). Other cytosolic actions may exist	**Distribution**: highly lipophilic, extensive tissue distribution, 98 % bound to plasma proteins **Metabolism**: extensively metabolized in liver at least partially by CYP3A4 **Excretion**: mainly fecal route (10 % unchanged in urine)	Used for prevention as monotherapy or treatment as an ACT Increased *pfmdr1* copy numbers associated with resistance (may increase import into digestive vacuole and create resistance if drug's main target is cytosolic)
Quinine/quinidine	Alkaloids of cinchona (powdered bark of South American cinchona tree)	Binds heme and prevents detoxification. Depresses oxygen uptake and carbohydrate metabolism. Intercalates into DNA which disrupts parasite's replication and transcription	**Absorption**: readily absorbed from oral or IM route (>80 % from GIT), Tmax = 3–8 h **Distribution**: apparent volume of 1.5 L/kg **Metabolism**: extensively metabolized by CYP3A4. Major metabolite 3-hydroxyquinine which maintains activity and can be toxic in renal failure **Elimination**: 20 % eliminated unchanged in urine	Acts on asexual erythrocytic forms with no effect on hepatic forms of malaria. Valuable for parenteral treatment of severe forms of resistant *P. falciparum*. Resistance correlated with some strains of resistance to chloroquine but also may be closer linked to mefloquine and halofantrine. Point mutations in *pfmdr1* can contribute to resistance (N1042D mutation)
Artemisinin	Sesquiterpene lactone endoperoxide derived from *qing hao (Artemisia annua)*	Reductive scission of peroxide bridge by reduced heme-iron produced inside digestive vacuole of the parasite as it digests hemoglobin. May also generate free radicals that alkylate and oxidize proteins and lipids in	**Absorption**: rapid, bioavailability ≤30 % after oral dosing. IM peak in 2–6 h (depot effect) **Distribution**: selective distribution into infected erythrocytes **Metabolism**: autoinduction via CYP2B6 and CYP3A4	Potent and fast acting. Rapidly clears parasites and resolve fever faster than any other marketed antimalarial. Effective for *P. falciparum* and asexual erythrocytic stages of *P. vivax*. Also demonstrates

		parasitized erythrocytes. Shown to inhibit nucleic acid and protein synthesis	**Elimination**: limited information available (see other artemisinin derivatives)	gametocytocidal activity. Cross-resistance not demonstrated with other drugs. However, emergence of *P. falciparum* with increased tolerance to artemisinin agents has been noted
Artemether	Lipophilic methyl ether	See artemisinin	**Absorption**: enhanced by food, Tmax = 2 h **Distribution**: 43–82 % bound to plasma proteins (95.4 % in vitro) **Metabolism**: extensively metabolized to DHA predominantly by CYP3A4/5 but also CYP2B6, CYP2C9, and CYP2C19 **Elimination**: artemether and DHA cleared from plasma with elimination t1/2 = 2 h. Only 0.01 % DHA found in urine (no traces of artemether)	First-line agent in combination with lumefantrine. See artemisinin above for other considerations
Artesunate	Water-soluble hemisuccinate ester of DHA	See artemisinin	**Absorption**: not affected by food **Distribution**: 43–82 % bound to plasma proteins, DHA concentrates in infected erythrocytes **Metabolism**: extensively metabolized to DHA largely by CYP2A6, Autoinduction via CYP2B6 and CYP3A4 **Elimination**: not fully investigated but findings suggest <1 % recovered as parent drug in urine, feces, and bile	Can be used first-line in combination with amodiaquine, sulfadoxine-pyrimethamine, or mefloquine. See artemisinin above for other considerations

(continued)

Table 2.1 (continued)

Drug	General chemistry	Mechanism of action	Clinical pharmacology	Clinical pharmacodynamics
Dihydroartemisinin	Reduced product of artemisinin	See artemisinin	Glucuronide conjugation	
Lumefantrine	Structurally similar to arylaminoalcohol drugs (mefloquine, halofantrine)	Not well defined. Suggested it inhibits formation of B-hematin by forming complex with hemin. Also shown to inhibit nucleic acid and protein synthesis	**Absorption**: increased by intake of high fat meal **Distribution**: large apparent volume of distribution **Metabolism**: metabolized mainly by CYP3A4 to desbutyl-lumefantrine **Elimination**: elimination t1/2 = 4–5 days. No trace found in urine	Formulated with artemether
Primaquine	8-aminiquinoline	Unknown. May be converted to electrophilic intermediates acting as oxidation-reduction mediators. This may lead to generation of reactive oxygen species or interference with mitochondrial electron transport	**Absorption**: almost complete absorption from gastrointestinal tract. Tmax = 3 h **Distribution**: extensive tissue distribution, resulting in high apparent volume of distribution. Binds to α1-glycoprotein **Metabolism**: rapidly metabolized. Induces CYP1A2 **Elimination**: excreted in urine with small fraction as parent drug	Active on exoerythrocytic tissue stages of plasmodia in liver. Prevents and cures relapsing malaria. Also displays gametocytocidal activity against *P. falciparum*. Inactive against asexual blood stage parasites. Exhibits high rates of hemolysis and not recommended for patients with G6PD deficiency. Some *P. vivax* strains have shown resistance to primaquine
Atovaquone	Highly lipophilic analog of ubiquinone	Acts selectively on mitochondrial cytochrome bc_1 complex to inhibit electron transport and collapse mitochondrial membrane potential	**Absorption**: slow, erratic and variable. Increases with consumption of fatty meal **Distribution**: >99 % bound to plasma proteins	Effective against liver stages of *P. falciparum* but not *P. vivax* liver hypnozoites. Synergy with proguanil results from its enhancement of mitochondrial

			Metabolism: minimal **Elimination**: excreted in bile and >94 % recovered unchanged in feces. Elimination t1/2 reported to be 2–3 days in adults and 1–2 days in children	toxicity of atovaquone. Resistance conferred by single non-synonymous nucleotide polymorphisms in cytochrome b gene within mitochondrial genome
Proguanil	Biguanide analog. Metabolized to cycloguanil (triazine)	Proguanil enhances collapsing of mitochondrial membrane by atovaquone but no activity on own. Cycloguanil selectively inhibits dihydrofolate reductase-thymidylate synthetase of sensitive plasmodia, causing inhibition of DNA synthesis and deletion of folate cofactors	**Absorption**: slow but adequate GI absorption (Tmax = 5 h) **Distribution**: accumulates in red blood cells (3× higher concentrations than in plasma) **Metabolism**: oxidized to cyclogunail and inactive 4-chlorophenylbiguanide. Prone to polymorphisms with CYP2C subfamily **Elimination**: 40–60 % (proguanil or cycloguanil) excreted in urine. 4-chlorophenylbiguanide excreted in urine, especially with poor proguanil metabolizers	Activity against both liver and asexual red blood cell stages in *P. falciparum*. Active against *P. vivax* but prone to relapses. Synergy occurs with atovaquone, as described above. Amino acid changes near dihydrofolate reductase-binding site confer resistance to cycloguanil. Cross-resistance occurs with pyrimethamine

ACT artemisinin-based combination therapy, *DHA* dihydroartemisinin, *G6PD* glucose-6-phosphate dehydrogenase, *IM* intramuscular, *P Plasmodium*, *pfcrt P. falciparum* chloroquine resistance transporter, *pfmdr1 P. falciparum* multi-drug resistant protein, *t1/2* half-life, *Tmax* time to maximum concentration

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Chapter 3
Drug Interaction Potential of Antimalarial Drugs Based on Known Metabolic Properties of Antimalarials

In this chapter, we describe the potential for drug interactions for various antimalarial drugs based on their known metabolic properties. These antimalarials include the following: chloroquine, amodiaquine, sulfadoxine and pyrimethamine, mefloquine, primaquine, atovaquone, proguanil, quinine, artemisinin, artesunate, artemether, and dihydroartemisin.

3.1 Chloroquine

In vitro reaction phenotyping studies have been carried out to determine the CYP450 enzymes responsible for the N-dealkylation of chloroquine in the formation of its major metabolite, desethylchloroquine. Using a panel of recombinant human CYP450 enzymes, Projean et al. (2003) and Kim et al. (2003) demonstrated the catalytic activity of CYP1A2, CYP2C8, CYP2C19, CYP2D6, and CYP3A4 in the formation of desethylchloroquine. However, using regression analysis with marker reactions in human liver microsomes, it was determined that desethylchloroquine formation correlated only with marker reactions for CYP3A4 (midazolam 1-hydroxylation or testosterone-6β-hydroxylation) and CYP2C8 (paclitaxel α-hydroxylation) (Projean et al. 2003; Kim et al. 2003). The roles of CYP3A4 and CYP2C8 were further supported by chemical inhibition assays with probe-selective chemical modulators (i.e. quercetin for CYP2C8 and ketoconazole or troleandomycin for CYP3A4 (Projean et al. 2003; Kim et al. 2003). These findings were corroborated with the relative activity factor approach, which also suggested a role for CYP2D6 in addition to CYP2C8 and CYP3A4 in the formation of desethylchloroquine (Li et al. 2003). As enzyme-specific immunoinhibitory antibodies were not in widespread use at the time these studies were conducted, these findings were based on industry standard reaction phenotyping approaches and the reported results were consistent between the different investigative groups. Also, in addition to being a substrate for CYP450 enzymes, chloroquine itself acts

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as a relatively weak inhibitor for CYP2D6 (ki (inhibition constant) = 12.4–15 μM) based on in vitro experiments from two separate studies (Bapiro et al. 2001; Masimirembwa et al. 1995). Taken together, it may be proposed that the co-administration of drugs that modulate CYP2C8, CYP3A4, and CYP2D6 could have potential effects on the pharmacokinetics of chloroquine; but, chloroquine, given its weak inhibitory activities, is unlikely to have an effect on the pharmacokinetics of other CYP2D6 substrates.

3.2 Amodiaquine

The primary metabolite of amodiaquine in humans, N-desethylamodiaquine, is predominately generated by CYP2C8, as demonstrated by a series of systematic in vitro reaction phenotyping studies conducted by Li et al. (2002). Using cDNA-expressed CYP450 isoenzymes, it was determined that CYP2C8, CYP1A1, CYP1B1, CYP2D6, and CYP3A4 were capable of oxidizing amodiaquine. A high degree of correlation with the 6-alpha hydroxylation of paclitaxel, a known marker reaction of CYP2C8, and the selective inhibition by quercetin, a potent inhibitor of the same isoenzyme, indicated the primary role of CYP2C8 (Li et al. 2002). These observations were supported by relative activity factor calculations that also demonstrated CYP2C8 as the primary enzyme responsible for the N-desethylation of amodiaquine (Li et al. 2002, 2003). Because of these well-established metabolic properties, amodiaquine N-desethylation is currently used as a marker reaction for CYP2C8 (Walsky et al. 2005).

A predominant role by CYP2C8 suggests that genetic polymorphisms or concurrent medications that inhibit this isoenzyme can potentially affect the clearance of amodiaquine in humans. Parikh et al. (2007) studied metabolic properties of amodiaquine using polymorphic CYP2C8 in vitro and found significant reductions in intrinsic clearance and maximal velocity (Vmax) and increased Km (concentration of substrate that results in half Vmax) with the CYP2C8*2 allele. The same authors also reported potent inhibitory effects by efavirenz, saquinavir, lopinavir, tipranavir, and ritonavir, based on IC50 (half maximal inhibitory concentration) values, toward the oxidation of amodiaquine in cDNA-expressed CYP2C8 supersomes. The clinical significance of these effects, however, remains to be determined in humans. On the other hand, amodiaquine is not known to be a potent inhibitor of major CYP450 enzymes. As demonstrated by Bapiro et al. (2001), amodiaquine inhibited (minimally) marker reactions for CYP1A2, CYP2C9, and CYP2C19 with the inhibition constant ranging from 26 to 46 μM, indicating a low likelihood of a clinically significant drug-drug interaction with amodiaquine being the offending agent.

3.3 Sulfadoxine and Pyrimethamine

Sulfadoxine undergoes minimal hepatic biotransformation and is unlikely to be subjected to clinically significant drug-drug interactions involving biotransformation. On the other hand, pyrimethamine is predominately metabolized hepatically, although the exact biochemical pathways remain to be characterized thereby limiting the predictability of clinically relevant drug interactions.

3.4 Mefloquine

Mefloquine is predominately cleared by hepatic metabolism and in vitro experiments in human hepatocytes and microsomes (Fontaine et al. 2000; Na-Bangchang et al. 1992) have indicated CYP3A4 as the primary isoenzyme responsible for its biotransformation. Fontaine et al. (2000) demonstrated increased formation of carboxy- and hydroxy-metabolites of mefloquine in dexamethasone (inducer of CYP3A4) pre-treated human hepatocytes. In further support of a role of this specific metabolic pathway, Fontaine et al. (2000) also demonstrated potent inhibition of mefloquine oxidation by ketoconazole (a selective CYP3A4 inhibitor) in rifampin (CYP3A4 inducer)-pretreated human hepatocytes, and reported a high degree of correlation between mefloquine oxidation activity and that of erythromycin N-demethylation, a marker reaction for CYP3A4 in human liver microsomes. Similar findings were obtained by Na-Bangchang et al. (1992) in human liver microsomes where ketoconazole was shown to extensively inhibit (inhibition constant = 11.2 μM) the formation of carboxymefloquine. These findings suggest that co-administered CYP3A4 modulators can potentially affect the clinical pharmacokinetics of mefloquine. On the other hand, little is known of the potential for mefloquine to cause drug interactions. It can serve as a competitive inhibitor of CYP3A4 by virtue of being a substrate of this enzyme, but little in vitro or preclinical data are available on the effects of mefloquine on other enzyme systems/pathways in humans.

3.5 Primaquine

Primaquine is primarily metabolized to carboxyprimaquine in humans. Jin et al. (2014) conducted a reaction phenotyping study using cultured human hepatocytes, recombinant CYP450 enzymes, monoamine oxidases, and flavin-containing monooxygenases, in conjunction with chemical inhibition experiments using in vitro setups. In cultured human hepatocytes, fluvoxamine (CYP1A2 inhibitor), quinidine (CYP2D6 inhibitor), ketoconazole (CYP3A4 inhibitor), clogyline (monoamine oxidase-A inhibitor), deprenyl (monoamine oxidase-B

inhibitor), and methimazole (flavin-containing monooxygenase inhibitor) were able to reduce (modestly) the degradation of primaquine under their experimental conditions. Incubations of primaquine with recombinant enzymes indicated that the same enzymes identified with chemical inhibition experiments (with more prominent effects from CYP2D6) were capable to catalyze the degradation of primaquine. A limitation, however, is that the formation of carboxyprimaquine was not determined; thus, one could not attribute the formation of this major metabolite to any of the identified metabolic pathways. In support of these findings, Na-Bangchang et al. (1992) also demonstrated, an extensive reduction of carboxyprimaquine formation by ketoconazole (CYP3A4 inhibitor) in human liver microsomes, further strengthening the role of CYP3A4 in this process. Taken together, these findings suggest that CYP2D6 and CYP3A4 may be the primary enzymes responsible for the metabolism (and the formation of carboxyprimaquine) in humans, although further reaction phenotyping studies using industry standard complementary approaches such as immunoreactive antibodies, correlational analyses, and relative activity factor determination are also needed to establish definitive conclusions. Furthermore, by virtue of primaquine being a substrate for CYP2D6 and CYP3A4, it may serve as a competitive inhibitor of these enzymes. In addition, there is suggestion that primaquine may activate CYP1A1, via the aryl hydrocarbon receptor (Fontaine et al. 1999), although further mechanistic studies are needed and it is unknown whether this inductive property of primaquine is associated with clinically relevant drug interactions.

3.6 Atovaquone

Atovaquone undergoes minimal hepatic/extra-hepatic biotransformation and is predominately excreted unchanged in feces (Rolan et al. 1997). These properties make it unlikely to be affected by interacting drugs and the available data also indicate that it does not affect the pharmacokinetics of other agents (Bapiro et al. 2001; Trapnell et al. 1998).

3.7 Proguanil

Proguanil in primarily metabolized to cycloguanil in humans. In vitro reaction phenotyping studies have been conducted by Birkett et al. (1994), Lu et al. (2000), and Coller et al. (1999) using human liver microsomes, cDNA-expressed supersomes, enzyme-selective chemical inhibitors, and enzyme-specific antibodies. All three studies were consistent in reporting, via their chemical inhibition, antibody inhibition, and correlational analysis experiments, a major role of CYP2C19 in the metabolism of proguanil. However, the same cannot be said for CYP3A4, where Lu et al. (2000) and Birkett et al. (1994) both reported significant

reductions in cycloguanil formation in the presence of troleandomycin (potent CYP3A4 inhibitor) whereas Coller et al. (1999) demonstrated little inhibition of proguanil metabolism in the presence of a CYP3A4-specific immunoantibody in human liver microsomes. Likewise, Lu et al. (2000) showed little effects of furafylline (CYP1A2 inhibitor) on the formation of cycloguanil, whereas Coller et al. (1999) demonstrated a significant decrease in biotransformation of proguanil using the same chemical inhibitor in human liver microsomes. The discrepancies with respect to CYP1A2 and CYP3A4 may be attributed to differences in in vitro experimental conditions or to differences between the ethnicity of donors of human liver microsomes (Lu et al. (2000) used liver microsomes from Chinese subjects). Taken together, these data suggest that concurrent medications that can modulate CYP2C19 may cause a clinically significant change in the pharmacokinetics of proguanil, but the roles of other CYP450 enzymes need to be clarified further with mechanistic studies. On the other hand, little data are available documenting the effects of proguanil as a causative agent of drug interactions. In an in vitro experiment, proguanil has been shown to lack inhibitory effects toward major CYP450 enzymes in humans (Bapiro et al. 2001).

3.8 Quinine

Quinine is primarily oxidized to 3-hydroxyquinine in humans. Zhao et al. (1996) characterized the CYP450 isoenzymes responsible for the 3-hydroxylation of quinine using various in vitro approaches. Using a panel of 9 recombinant CYP450 isoenzymes, only CYP2C19 and CYP3A4 catalyzed the formation of 3-hydroxyquinine. These findings were supported by significant correlations between the 3-hydroxylation of quinine and the 6-beta hydroxylation of testosterone, a marker reaction for CYP3A4, and 4′-hydroxylation of S-mephenytoin, a marker reaction for CYP2C19. Definitive reaction phenotyping was obtained by using ketoconazole, troleandomycin (selective and potent inhibitor for CYP3A4), and CYP3A4-specific inhibitory antibodies which caused extensive reductions in 3-hydroxy quinine formation in human liver microsomes, indicating a major role of this isoenzyme in the metabolism of quinine. More modest reductions in 3-hydroxy quinine formation in the presence of S-mephenytoin (selective chemical inhibitor of CYP2C19) or CYP2C-specific immunoinhibitory antibody suggested a minor, but significant, contribution of CYP2C19 toward the oxidation of quinine. These findings are supported by relative activity factor calculations conducted by Li et al. (2003) who also suggested a major contribution by CYP3A4 and a minor contribution by CYP2C19 toward the formation of 3-hydroxyquinine. By virtue of being a major substrate for CYP3A4, quinine is subjected to drug-drug interactions. In human liver microsomes, Zhao and Ishizaki (1997, 1999) characterized the inhibitory effects of various drugs on the 3-hydroxylation of quinine and found that ketoconazole, doxycycline, omeprazole, and tetracycline (inhibition constant <7.3 μM) were relatively potent inhibitors of the reaction. On the other hand,

quinine itself can also cause drug-drug interactions. In vitro, it is known to inhibit CYP2D6 (Bapiro et al. 2001) with relatively high potency (inhibition constant = 4.77 μM) which may also translate to clinically relevant pharmacokinetic drug interactions.

3.9 Artemisinin

Artemisinin is primarily metabolized in humans by CYP450 enzymes. Svensson and Ashton (1999) conducted reaction phenotyping studies to determine the contribution of individual CYP450 enzymes in the disappearance of artemisinin from reaction media in various in vitro models. Using a panel of cDNA-expressed enzymes, CYP2B6 had the highest catalytic activity, followed by CYP2A6 and CYP3A4. Chemical inhibition experiments using orphenadrine (a CYP2B6-selective inhibitor) in human liver microsomes further supported the predominant role of CYP2B6 in the biotransformation of artemisinin. As neither ketoconazole (CYP3A4 inhibitor) nor 8-methoxypsoralen (CYP2A6 inhibitor) completely reduced the disappearance of artemisinin from the incubation medium in human liver microsomes, it may be concluded that these two CYP450 isoenzymes play a relatively minor role (compared to CYP2B6) in the hepatic metabolism of artemisinin. These findings were further supported by relative activity factor calculations conducted by Li et al. (2003) that illustrated contributions by the same isoenzymes and suggest potential clinically relevant drug interactions caused by drugs known to modulate these metabolic pathways. On the other hand, artemisinin itself is known to inhibit CYP1A2 with relatively high potency in vitro (Bapiro et al. 2001) and has been demonstrated in various experimental models to be an inducer of CYP2C19 and CYP2B6 which may partially explain its autoinductive properties in human (Elsherbiny et al. 2008; Simonsson et al. 2003; Svensson et al. 1998).

3.10 Artesunate

Artesunate is bioactivated to dihydroartemisinin via esterases and CYP450 enzymes. Using a panel of recombinant CYP450 enzymes, Li et al. (2003) demonstrated the catalytic activities of CYP2A6, CYP1B1, CYP2B6, CYP2E1, and CYP4A11 in the biotransformation of artesunate in vitro. However, additional calculations using the relative activity factor approach, which incorporates reaction rates determined from recombinant CYP450 enzymes and the relative content of each CYP450 enzyme in human liver microsomes, indicated that only CYP2A6 contributed to the metabolism of artesunate, and thus may be subjected to drug interactions involving modulators of this isoenzyme. On the other hand, artesunate has virtually no inhibitory activities toward various major CYP450 isoenzymes, as

demonstrated in vitro by Bapiro et al. (2001) and little is known about its inductive properties toward other metabolic pathways.

3.11 Artemether

Artemether is also bioactivated to the more potent dihydroartemisinin by CYP450 enzymes in humans as demonstrated in in vitro reaction phenotyping studies conducted by Grace et al. (1998). Using an extensive panel of recombinant CYP450 enzymes, only CYP3A4, CYP3A5, and CYP2B6 were capable of catalyzing the formation of dihydroartemisinin with the catalytic activity of CYP3A4 being about 4- to 10-fold of that of CYP3A5 and CYP2B6, respectively. In human liver microsomes co-incubated with artemether and various CYP450-selective chemical inhibitors, only ketoconazole and troleandomycin (CYP3A4-selective inhibitors) and SKF-525 (a broad-spectrum CYP450 inhibitor) were able to reduce the formation of dihydroartemisinin by ~70 %, indicating a major role of CYP3A4 in the bioactivation of artemether. Furthermore, mefloquine and quinidine, both CYP3A4 substrates, were shown to inhibit dihydroartemisinin formation in select human liver microsomes. Although the study did not utilize enzyme-specific immunoinhibitory antibodies, these results support a major role for CYP3A4 and suggest that inducers or inhibitors of this isoenzyme may be associated with clinically relevant drug-drug interactions.

3.12 Dihydroartemisinin

Dihydroartemisinin is the predominant bioactivation product of artemether and artesunate, and the responsible pathways have been discussed above. Dihydroartemisinin itself is further metabolized/deactivated by phase II conjugation via Uridine 5′-diphospho-(UDP)-glucuronosyltransferase (UGT)-1A9 and UGT2B7 (Ilett et al. 2002). However, this conclusion was drawn only from experiments conducted with expressed UGT enzymes that showed catalytic activities with these two isoenzymes. The lack of chemical or immunoinhibitory experiments in this study and the standard approaches in current reaction phenotyping studies preclude further conclusions about the relative contributions of either UGT enzyme. Furthermore, there is a general lack of information, to our knowledge, on the role of other enzymatic pathways (e.g. phase I, II, or III enzymes) on the metabolism of dihydroartemisinin in humans. Therefore, further studies are needed to elucidate the metabolic pathways for this critical, potent metabolite of currently used artemisinin derivatives.

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Chapter 4
Pharmacokinetic Drug Interactions Affecting Antimalarials

This chapter provides details of studies that describe drug interactions affecting the pharmacokinetics of various antimalarial drugs, including amodiaquine, artemether/lumefantrine, artemisinin derivatives, atovaquone, chloroquine, mefloquine, proguanil, and quinine.

4.1 Effects of Drugs on the Pharmacokinetics of Amodiaquine

Scarsi et al. (2014) studied the effects of steady-state nevirapine (200 mg)-based antiretroviral therapy containing zidovudine (300 mg) and lamivudine (150 mg) on the pharmacokinetics of amodiaquine and desethylamodiaquine in HIV-infected, but malaria-free, individuals using an open label, parallel control group design. Subjects received the combination of artesunate/amodiaquine (200/600 mg) orally daily for 3 days, but only the pharmacokinetics of amodiaquine and its major metabolite desethylamodiaquine were quantified. The major finding was that nevirapine-based antiretroviral therapy significantly reduced the exposures of both amodiaquine (204 vs. 145 ng h/mL, mean) and desethylamodiaquine (21,648 vs. 14,571 ng h/mL) compared to the nevirapine-naïve control group, respectively. No other pharmacokinetic differences were observed (i.e. maximum concentration (Cmax), time to reach maximum concentration (Tmax), area under the curve (AUC)metabolite/AUCamodiaquine ratio) for desethylamodiaquine but significant changes in Cmax (16.7 vs. 24.6 ng/mL, mean), Tmax (1 vs. 3 h), apparent oral clearance (CL/F) (4,165 vs. 2,775 L/h), apparent volume of distribution (Vd/F) (63,761 vs. 25,837 L) were observed for subjects receiving nevirapine compared to the controls, respectively. Nevirapine, being an inducer of Cytochrome P450 (CYP)3A4 and CYP2B6 (Lamson et al. 1999), could not have decreased the exposure of amodiaquine since it is known to be predominately

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metabolized by a single CYP2C8 pathway. Likewise, neither zidovudine nor lamivudine is known to affect CYPP450 metabolism, suggesting that other metabolic processes or pathways of amodiaquine or desethylamodiaquine, which remain to be determined, may have contributed to these findings. These data, however, should be interpreted in the context of some limitations of the study (i.e. small sample size, baseline differences between study groups, etc.), and it is not clear whether these findings can be generalized to the true patient population, because one must consider the interaction between malaria itself and the pharmacokinetics of these agents (Table 4.1).

4.2 Effects of Drugs on the Pharmacokinetics of Artemether/Lumefantrine

van Agtmael et al. (1998) studied the effects of single oral doses of quinidine (50 mg) or omeprazole (40 mg on the pharmacokinetics of artemether (100 mg orally × 1) and its metabolite, dihydroartemisinin, in healthy male volunteers (n = 7) of Dutch ethnicity using an open-label, prospective, cross over design. Neither quinidine nor omeprazole significantly affected the AUC, Cmax, Tmax, Vd/F, and half life (t1/2) of artemether or dihydroartemisinin (no absolute values provided in the co-administration group). Artemether is primarily metabolized by CYP3A4 (German and Aweeka 2008) but also can be catalyzed by CYP2B6, CYP2C9, or CYP2C19 (minor contribution), which may explain the lack of inhibition by quinidine, a CYP2D6 inhibitor (Speirs et al. 1986), or omeprazole, a CYP2C19 inhibitor (Balian et al. 1995), in this particular study. However, one should interpret the negative findings from this study in the context of single-dose (non-steady state) design in a non-diseased male population with relatively small sample size and large variability.

Lamorde et al. (2013) compared the pharmacokinetics of artemether-lumefantrine (given 80/480 mg orally twice daily for 3 days) in the presence or absence of rifampin (in combination with other medications, dosing information not provided) as part of a steady-state tuberculosis treatment using an open-label, prospective, cross over design in Ugandan patients (n = 5–6). The presence of rifampin significantly reduced the AUC (89 %, 90 % confidence interval 5–26 %) and Cmax (83 %, 8–39 %) of artemether, decreased the AUC (85 %, 10–23 %) and Cmax (78 %, 15–33 %) of dihydroartemisinin, and reduced the AUC (84 %, 9–27 %) and day 8 concentration (84 %, 9–27 %) of lumefantrine. Although t1/2 values were reported, they did not appear to be significantly different between treatments for any of the analytes. No other pharmacokinetic parameters were reported by the authors. These findings are consistent with the known metabolic properties of the interacting agents: that artemether is primarily metabolized by CYP3A4 (German and Aweeka 2008) but also can be catalyzed by CYP2B6, CYP2C9, or CYP2C19 (minor contribution), lumefantrine is primarily metabolized

Table 4.1 Effects of co-administered drugs on pharmacokinetics of antimalarials

	Population	Design	N	Effect drug dosing	Affect drug dosing	Effects of drug on antimalarial/metabolite PK								Reference
						Analyte	AUC	Cmax	Cmin	Tmax	Vd/F	CL/F	t1/2	
Nevirapine (+zidovudine/ lamivudine)	HIV + but malaria free Age: 39.7 vs. 35.8 (control) years Wt: ND	Open label Prospective Parallel group	10 (nevirapine) 11 (control)	Nevirapine (200 mg), zidovudine (300 mg), lamivudine (150 mg) orally twice daily × minimum 8 weeks (steady-state)	200/600 mg (artesunate/ amodiaquine) orally daily × 3 days	Amodiaquine	↓(29 %)	↔	ND	↓(67 %)	↑(146 %)	↑(50 %)	↔	Scarsi et al. (2014)
Nevirapine (+zidovudine/ lamivudine)	HIV + but malaria free Age: 39.7 vs. 35.8 (control) years Wt: ND	Open label Prospective Parallel group	10 (nevirapine) 11 (control)	Nevirapine (200 mg), zidovudine (300 mg), lamivudine (150 mg) orally twice daily × minimum 8 weeks (steady-state)	200/600 mg (artesunate/ amodiaquine) orally daily × 3 days	Amodiaquine (desethylamodiaquine)	↓(33 %)	↔	ND	↔	ND	ND	ND	Scarsi et al. (2014)
Omeprazole	Healthy male volunteers of Dutch ethnicity Age: 19–26 years old Wt: 65–90 kg	Open label Prospective Cross over	7	100 mg orally × 1	40 mg orally × 1	Artemether	↔	↔	ND	↔	↔	ND	↔	van Agtmael et al. (1998)
Omeprazole	Healthy male volunteers of Dutch ethnicity Age: 19–26 years old Wt: 65–90 kg	Open label Prospective Cross over	7	100 mg orally × 1	40 mg orally × 1	Artemether (dihydroartemisinin)	↔	↔	ND	↔	↔	ND	↔	van Agtmael et al. (1998)
Rifampin	HIV-positive Ugandan undergoing TB treatment but without malaria	Open label Prospective Cross over (from rifampin-	5–6	80 mg/480 mg (artemether/ lumefantrine) orally twice daily for 3 days	Steady-state dosing of rifampin (with other TB medications)—no dosing specified	Artemether-lumefantrine (artemether)	↓(89 %)	↓(83 %)	ND	ND	ND	ND	↔	Lamorde et al. (2013)

(continued)

Table 4.1 (continued)

	Population	Design	N	Effect drug dosing	Affect drug dosing	Effects of drug on antimalarial/metabolite PK								Reference
						Analyte	AUC	Cmax	Cmin	Tmax	Vd/F	CL/F	t1/2	
		based TB treatment to no-rifampin TB treatment)												
Rifampin	HIV-positive Ugandan undergoing TB treatment but without malaria	Open label Prospective Cross over (from rifampin-based TB treatment to no-rifampin TB treatment)	5–6	80 mg/480 mg (artemether/lumefantrine) orally twice daily for 3 days	Steady-state dosing of rifampin (with other TB medications)—no dosing specified	Artemether-lumefantrine (dihydroartemisinin)	↓(85 %)	↓(78 %)	ND	ND	ND	ND	↔	Lamorde et al. (2013)
Rifampin	HIV-positive Ugandan undergoing TB treatment but without malaria	Open label Prospective Cross over (from rifampin-based TB treatment to no-rifampin TB treatment)	5–6	80 mg/480 mg (artemether/lumefantrine) orally twice daily for 3 days	Steady-state dosing of rifampin (with other TB medications)—no dosing specified	Artemether-lumefantrine (lumetantrine)	↓(68 %)	ND	ND	ND	ND	ND	↔	Lamorde et al. (2013)
Ketoconazole	Healthy Caucasian subjects Age: 19–49 years old Wt: 61.4–87.4 kg	Open label Prospective Randomized Cross over	16	80 mg/480 mg (artemether/lumefantrine) orally × 1	400 mg orally × 1, then 200 mg daily for 4 days	Artemether-lumefantrine (artemether)	↑(140 %)	↑(120 %)	ND	↔	ND	ND	↑(32 %)	Lefevre et al. (2002)
Ketoconazole	Healthy Caucasian subjects Age: 19–49 years old Wt: 61.4–87.4 kg	Open label Prospective Randomized Cross over	16	80 mg/480 mg (artemether/lumefantrine) orally × 1	400 mg orally × 1, then 200 mg daily for 4 days	Artemether-lumefantrine (dihydroartemisinin)	↑(70 %)	↑(40 %)	ND	↔	ND	ND	↔	Lefevre et al. (2002)

Ketoconazole	Healthy Caucasian subjects Age: 19–49 years old Wt: 61.4–87.4 kg	Open label Prospective Randomized Cross over	16	80 mg/480 mg (artemether/ lumefantrine) orally × 1	400 mg orally × 1, then 200 mg daily for 4 days	Artemether-lumefantrine (lumefantrine)	↑(70 %)	↔	ND	↔	ND	ND	↔	Lefevre et al. (2002)
Trimethoprim-sulfamethoxazole	HIV-infected (5 M) Age: 31 years (median)	Open label Prospective Cross over	6	160/800 mg orally every 12 h × 1 week	500 mg orally daily (with food) × 2 weeks	Atovaquone	ND (see text)	ND	ND	ND	ND	ND	ND	Falloon et al. (1999)
Efavirenz	Healthy vs. - HIV-infected on HIV-antiviral Age: 18–65 years	Open label Prospective	18 (Healthy) 20 (HIV)	250 mg atovaquone + 100 mg proguanil orally × 1 dose (prophylactic dose)	Steady-state 600 mg orally daily	Atovaquone	↓(75 %)	↓(44 %)	ND	ND	ND	ND	ND	van Luin et al. (2010)
Lopinavir/ Ritonavir	Healthy vs. - HIV-infected on HIV-antiviral Age: 18–65 years	Open label Prospective	18 (Healthy) 19 (HIV)	250 mg atovaquone + 100 mg proguanil orally × 1 dose (prophylactic dose)	Steady-state 800/200 mg lopinavir/ritonavir orally daily	Atovaquone	↓(74 %)	↓(44 %)	ND	ND	ND	ND	ND	van Luin et al. (2010)
Atazanavir/ Ritonavir	Healthy vs. HIV-infected on HIV-antiviral Age: 18–65 years	Open label Prospective	18 (Healthy) 19 (HIV)	250 mg atovaquone + 100 mg proguanil orally × 1 dose (prophylactic dose)	300/100 mg atazanavir/ritonavir orally daily	Atovaquone	↓(44 %)	↓(49 %)	ND	ND	ND	ND	ND	van Luin et al. (2010)
Cimetidine	Healthy (all M) Age: 21–27 years old Wt: 63–68 kg	Open label Prospective Randomized Parallel control group	5	600 mg orally × 1	400 mg orally daily × 4 days	Chloroquine	ND	ND	ND	ND	↑(57 %)	↓(53 %)	↑(49 %)	Ette et al. (1987a)
Cimetidine	Healthy (all M) Age: 21–27 years old Wt: 63–68 kg	Open label Prospective Randomized Parallel control group	5	600 mg orally × 1	400 mg orally daily × 4 days	Chloroquine (monodesethyl-chloroquine)	↓(47 %)	↔	ND	↔	ND	ND	ND	Ette et al. (1987a)

(continued)

Table 4.1 (continued)

	Population	Design	N	Effect drug dosing	Affect drug dosing	Effects of drug on antimalarial/metabolite PK								Reference
						Analyte	AUC	Cmax	Cmin	Tmax	Vd/F	CL/F	t1/2	
Ranitidine	Healthy (all M) Age: 19–27 years old	Open label Prospective Randomized Parallel control group	5	600 mg orally × 1	250 mg orally daily × 4 days	Chloroquine	↔	ND	ND	ND	↔	↔	↔	Ette et al. (1987b)
Imipramine	Healthy volunteers Age: 23–28 years old Wt: 55–65 kg	Open label Prospective Randomized Cross over	6	300 mg orally × 1	50 mg orally × 1	Chloroquine	ND	↔	ND	↔	↔	↔	↔	Onyeji et al. (1993)
Aspirin	Healthy volunteers (all M)	Open label Prospective Cross over	8	600 mg orally × 1	325 mg orally × 1	Chloroquine	↔	↔	ND	ND	ND	ND	↔	Raina et al. (1993)
Acetaminophen	Healthy volunteers (all M)	Open label Prospective Cross over	8	600 mg orally × 1	500 mg orally × 1	Chloroquine	↑(23 %)	↑(17 %)	ND	ND	ND	ND	↔	Raina et al. (1993)
Analgin	Healthy volunteers (all M)	Open label Prospective Cross over	8	600 mg orally × 1	500 mg orally × 1	Chloroquine	↑(21 %)	↑(25 %)	ND	ND	ND	ND	↔	Raina et al. (1993)
Methylene blue	Healthy volunteers	Prospective Randomized Placebo-controlled Parallel group	24	130 mg orally twice daily × 3 days	40 mg/kg orally daily × 3 doses (1,000 mg × 1 day + 500 mg × 2 days for M patients; 750 mg × 1 day + 375 mg × 3 days for F patients)	Chloroquine	↔	ND	ND	ND	ND	ND	↔	Rengelshausen et al. (2004)
Methylene blue	Healthy volunteers	Prospective Randomized Placebo-controlled Parallel group	24	130 mg orally twice daily × 3 days	40 mg/kg orally daily × 3 doses (1,000 mg × 1 day + 500 mg × 2 days for M patients; 750 mg × 1 day + 375 mg × 3 days for F patients)	Chloroquine (desethylchloroquine)	↓(30 %)	ND	ND	ND	ND	ND	↔	Rengelshausen et al. (2004)

Azithromycin	Healthy volunteers	Open label Prospective Parallel groups	24 vs. 15 (control)	1 g orally × 2 days, then 500 mg orally × 1 day	1 g orally daily × 3 days	Chloroquine	↔	↔	ND	ND	ND	ND	↔	Cook et al. (2006)
Azithromycin	Healthy volunteers	Open label Prospective Parallel groups	24 vs. 15 (control	1 g orally × 2 days, then 500 mg orally × 1 day	1 g orally daily × 3 days	Chloroquine (desethylchloroquine)	↔	↔	ND	ND	ND	ND	↔	Cook et al. (2006)
Promethazine	Healthy volunteers	Open label Prospective Parallel groups	5	10 mg/kg orally daily on days 1 & 2, and 5 mg/kg orally × 1 on day 3	25 mg orally × 1, then 12.5 mg orally Q8H × 5 days	Chloroquine	↔	↔	ND	↔	ND	ND	↔	Gbotosho et al. (2008)
Chlorpheiramine	Healthy volunteers	Open label Prospective Parallel groups	5	10 mg/kg orally daily on days 1 & 2, and 5 mg/kg orally × 1 on day 3	8 mg orally × 1, then 4 mg orally Q8H × 7 days	Chloroquine	↔	↔	ND	↔	ND	ND	↔	Gbotosho et al. (2008)
Promethazine	Healthy volunteers	Open label Prospective Parallel groups	5	10 mg/kg orally daily on days 1 & 2, and 5 mg/kg orally × 1 on day 3	25 mg orally × 1, then 12.5 mg orally Q8H × 5 days	Chloroquine (in erythrocyte)	↔	↔	ND	↔	ND	ND	↔	Gbotosho et al. (2008)
Chlorpheiramine	Healthy volunteers	Open label Prospective Parallel groups	5	10 mg/kg orally daily on days 1 & 2, and 5 mg/kg orally × 1 on day 3	8 mg orally × 1, then 4 mg orally Q8H × 7 days	Chloroquine (in erythrocyte)	↑(114 %)	↑(24 %)	ND	↔	ND	ND	↑(96 %)	Gbotosho et al. (2008)
Metoclopramide	Healthy male volunteers Age: 24–44 years Wt: 47–60 kg	Open label Prospective Cross over	7	750 mg orally × 1	10 mg orally × 1	Mefloquine	↔	↑(31 %)	ND	ND	ND	ND	↔	Na-Bangchang et al. (1991)
Ampicillin	Healthy male Thai volunteers Age: 24–51 years Wt: 48–61 kg	Open label Prospective Cross over	8	750 mg orally × 1	250 mg orally 4 times daily for 5 days	Mefloquine	↔	↑(34 %)	ND	↔	↓(27 %)	↔	↓(14 %)	Karbwang et al. (1991)
Tetracycline	Healthy mail Thai volunteers Age: 19–43 years Wt: 49–68 kg	Open label Prospective Randomized Parallel control	11 (vs. 9 in control group)	750 mg orally × 1	250 mg orally four times daily for 7 days	Mefloquine	↔	↑(38 %)	ND	↔	↓(33 %)	↔	↓(25 %)	Karbwang et al. (1992)

(continued)

Table 4.1 (continued)

	Population	Design	N	Effect drug dosing	Affect drug dosing	Effects of drug on antimalarial/metabolite PK								Reference
						Analyte	AUC	Cmax	Cmin	Tmax	Vd/F	CL/F	t1/2	
Cimetidine	Healthy male volunteers Age: 32.2 ± 2.6 years (mean ± SD) Wt: 64.8 ± 6.0 kg	Open label Prospective Cross over	6	500 mg orally × 1	400 mg orally twice daily for 3 days	Mefloquine	↑(38 %)	↑(42 %)	ND	↔	↔	↔	↔	Kolawole et al. (2000)
Cimetidine	Patients with ulcer Age: 34.8 ± 3.9 years (mean ± SD) Wt: 65 ± 2.1 kg	Open label Prospective Cross over	6	500 mg orally × 1	400 mg orally twice daily for 3 days	Mefloquine	↑(32 %)	↑(21 %)	ND	↔	↔	↔	↔	Kolawole et al. (2000)
Rifampin	Healthy Thai male volunteers Age: 24–35 years Wt: 57–72 kg	Open label Prospective Cross over	7	500 mg orally × 1	Steady-state 600 mg orally daily for 7 days then twice weekly for total of 56 days	Mefloquine	↓(68 %)	↓(19 %)	ND	↔	ND	↑(281 %)	↓(63 %)	Ridtitid et al. (2000)
Rifampin	Healthy Thai male volunteers Age: 24–35 years Wt: 57–72 kg	Open label Prospective Cross over	7	500 mg orally × 1	Steady-state 600 mg orally daily for 7 days then twice weekly for total of 56 days	Mefloquine (carboxylic acid metabolite)	↔	↑(47 %)	ND	↓(76 %)	ND	↔	↓(39 %)	Ridtitid et al. (2000)
Ketoconazole	Healthy Thai male volunteers Age: 29.5 ± 8.4 years Wt: 61.5 ± 2.6 kg	Open label Prospective Randomized Cross over	8	500 mg orally × 1	400 mg orally daily for 10 days	Mefloquine	↑(79 %)	↑(64 %)	ND	↔	ND	ND	↑(39 %)	Ridtitid et al. (2005)
Ketoconazole	Healthy Thai male volunteers Age: 29.5 ± 8.4 years Wt: 61.5 ± 2.6 kg	Open label Prospective Randomized Cross over	8	500 mg orally × 1	400 mg orally daily for 10 days	Mefloquine (carboxylic acid metabolite)	↓(28 %)	↓(31 %)	ND	↔	ND	ND	↔	Ridtitid et al. (2005)
Ritonavir	Healthy volunteers	Open label Prospective Cross over	12	250 mg orally daily for 3 days, then once weekly for 4 weeks	200 mg orally twice daily for 7 days, then same dose again for 7 days with last mefloquine dose	Mefloquine	↔	↔	ND	ND	ND	↔	ND	Khaliq et al. (2001)

Ritonavir	Healthy volunteers	Open label Prospective Cross over	12	250 mg orally daily for 3 days, then once weekly for 4 weeks	200 mg orally twice daily for 7 days, then same dose again for 7 days with last mefloquine dose	Mefloquine (+) RS Mefloquine	↔	↔	ND	ND	ND	↔	ND	Khaliq et al. (2001)
Ritonavir	Healthy volunteers	Open label Prospective Cross over	12	250 mg orally daily for 3 days, then once weekly for 4 weeks	200 mg orally twice daily for 7 days, then same dose again for 7 days with last mefloquine dose	Mefloquine (-) SR Mefloquine	↔	↔	ND	ND	ND	↔	ND	Khaliq et al. (2001)
Ritonavir	Healthy volunteers	Open label Prospective Cross over	12	250 mg orally daily for 3 days, then once weekly for 4 weeks	200 mg orally twice daily for 7 days, then same dose again for 7 days with last mefloquine dose	Mefloquine (carboxylic acid metabolite)	↔	↔	ND	ND	ND	ND	ND	Khaliq et al. (2001)
Efavirenz	Healthy vs. - HIV-infected on HIV-antiviral Age: 18–65 years	Open label Prospective	18 (Healthy) 20 (HIV)	250 mg atovaquone + 100 mg proguanil orally × 1 dose (prophylactic dose)	Steady-state 600 mg orally daily	Proguanil	↓(43 %)	↔	ND	ND	ND	ND	ND	van Luin et al. (2010)
Lopinavir/ Ritonavir	Healthy vs. - HIV-infected on HIV-antiviral Age: 18–65 years	Open label Prospective	18 (Healthy) 19 (HIV)	250 mg atovaquone + 100 mg proguanil orally × 1 dose (prophylactic dose)	Steady-state 800/200 mg lopinavir/ritonavir orally daily	Proguanil	↓(38 %)	↔	ND	ND	ND	ND	ND	van Luin et al. (2010)
Atazanavir/ Ritonavir	Healthy vs. - HIV-infected on HIV-antiviral Age: 18–65 years	Open label Prospective	18 (Healthy) 19 (HIV)	250 mg atovaquone + 100 mg proguanil orally × 1 dose (prophylactic dose)	300/100 mg atazanavir/ritonavir orally daily	Proguanil	↓(41 %)	↔	ND	ND	ND	ND	ND	van Luin et al. (2010)

(continued)

Table 4.1 (continued)

	Population	Design	N	Effect drug dosing	Affect drug dosing	Effects of drug on antimalarial/metabolite PK								Reference
						Analyte	AUC	Cmax	Cmin	Tmax	Vd/F	CL/F	t1/2	
Omeprazole	Healthy Volunteers	Open label Prospective Cross over	12	200 mg orally × 1	40 mg orally daily × 7 days	Proguanil	↑(49 %)	ND	ND	ND	ND	↓(47 %)	↑(26 %)	Funck-Brentano et al. (1997)
Omeprazole	Healthy Volunteers	Open label Prospective Cross over	12	200 mg orally × 1	40 mg orally daily × 7 days	Proguanil (cycloguanil)	↓(47 %)	ND	ND	ND	ND	ND	ND	Funck-Brentano et al. (1997)
Cimetidine	Healthy volunteers Age: 28.67 ± 5.75 years (mean ± SD) Wt: 70.67 ± 1.51 kg	Open label Prospective Cross over	6	200 mg orally × 1	400 mg orally twice daily × 2.5 days	Proguanil	↑(93 %)	↑(89 %)	ND	↔	↔	↔	↑(48 %)	Kolawole et al. (1999)
Cimetidine	Healthy volunteers Age: 28.67 ± 5.75 years (mean ± SD) Wt: 70.67 ± 1.51 kg	Open label Prospective Cross over	6	200 mg orally × 1	400 mg orally twice daily × 2.5 days	Proguanil (cycloguanil)	↓(37 %)	↓(59 %)	ND	↔	ND	ND	ND	Kolawole et al. (1999)
Cimetidine	Male patients with peptic ulcer Age: 37.75 ± 1.26 years (mean ± SD) Wt: 68.5 ± 2.9 kg	Open label Prospective Cross over	4	200 mg orally × 1	400 mg orally twice daily × 2.5 days	Proguanil	↑(47 %)	↔	ND	↔	↔	↔	↑(62 %)	Kolawole et al. (1999)
Cimetidine	Male patients with peptic ulcer Age: 37.75 ± 1.26 years (mean ± SD) Wt: 68.5 ± 2.9 kg	Open label Prospective Cross over	4	200 mg orally × 1	400 mg orally twice daily × 2.5 days	Proguanil (cycloguanil)	↔	↓(33 %)	ND	↔	ND	ND	ND	Kolawole et al. (1999)
Efavirenz	Healthy volunteers (10 M) Age: 22–30 years Wt: 56–71 kg	Open label Prospective Cross over	15	300 mg orally × 1	400 mg orally daily × 11 days (steady-state)	Proguanil	↑(112 %)	↑(47 %)	ND	↑(71 %)	ND	↓(20 %)	↑(41 %)	Soyinka et al. (2010)

Efavirenz	Healthy volunteers (10 M) Age: 22–30 years Wt: 56–71 kg	Open label Prospective Cross over	15	300 mg orally × 1	400 mg orally daily × 11 days (steady-state)	Proguanil (cycloguanil)	↓(37 %)	↓(31 %)	ND	↑(23 %)	ND	ND	ND	Soyinka et al. (2010)
Doxycycline	Patients with acute falciparum malaria	Open label Prospective parallel group	13 (control) 13 (combination)	20 mg/kg infusion for 4 h, 15 mg/kg infusion for 20 h, then 25 mg/kg/day infusion for 2 more days	200 mg orally daily × 3 days	Quinine	ND	ND	ND	ND	↔	↔	↔	Couet et al. (1991)
Oral contraceptive	Thai female subjects on oral contraceptive Age: 19–35 years	Open label Prospective Parallel group of control not on oral contraceptive	7 in each group	600 mg orally × 1	Various oral contraceptive pills containing various forms of estrogen/progestin (steady-state dosing for 6 months)	Quinine	↔	↔	ND	↔	ND	↔	↔	Wanwimolruk et al. (1991)
Rifampin	Healthy Thai volunteers (all M)	Open label Prospective Randomized Cross over	9	600 mg orally × 1	600 mg orally daily × 2 weeks	Quinine	↓(83 %)	↓(52 %)	ND	↔	ND	↑(521 %)	↓(50 %)	Wanwimolruk et al. (1995)
Isoniazid	Healthy Thai volunteers (all M)	Open label Prospective Randomized Cross over	9	600 mg orally × 1	300 mg orally daily × 1 week	Quinine	↔	↔	ND	↔	ND	↔	↔	Wanwimolruk et al. (1995)
Rifampin	Patients with uncomplicated falciparum malaria (all M) Age: 24.2 ± 8.7 years (mean ± SD)	Open label Prospective Randomized Parallel group	29 vs. 30 (control)	10 mg/kg orally 3 times daily × 7 days	Rifampin 15 mg/kg/day for 7 days	Quinine	↓(75 %)	↔	ND	↓(67 %)	ND	ND	ND	Pukrittayakamee et al. (2003)
Rifampin	Patients with uncomplicated falciparum malaria (all M) Age: 24.2 ± 8.7 years (mean ± SD)	Open label Prospective Randomized Parallel group	29 vs. 30 (control)	10 mg/kg orally 3 times daily × 7 days	Rifampin 15 mg/kg/day orally for 7 days	Quinine (3-OH chloroquine)	See text	↑(34 %)	ND	↓(56 %)	ND	ND	ND	Pukrittayakamee et al. (2003)

(continued)

Table 4.1 (continued)

	Population	Design	N	Effect drug dosing	Affect drug dosing	Effects of drug on antimalarial/metabolite PK								Reference
						Analyte	AUC	Cmax	Cmin	Tmax	Vd/F	CL/F	t1/2	
Nevirapine	Healthy volunteers (8 M) Age: 19–27 years Wt: 49–67 kg	Open label Prospective Randomized Cross over	14	600 mg orally × 1	Steady-state 200 mg orally every 12 h	Quinine	↓(33 %)	↓(36 %)	ND	↔	ND	↑(50 %)	↓(25 %)	Soyinka et al. (2009)
Nevirapine	Healthy volunteers (8 M) Age: 19–27 years Wt: 49–67 kg	Open label Prospective Randomized Cross over	14	600 mg orally × 1	Steady-state 200 mg orally every 12 h × 12 days	Quinine (3-OH chloroquine)	↑(26 %)	↑(25 %)	ND	↔	ND	ND	ND	Soyinka
Ritonavir	Healthy volunteers	Open label Prospective Cross over	10	600 mg orally × 1	Steady-state 200 mg orally every 12 h × 9 days	Quinine	↑(340 %)	↑(284 %)	ND	↔	ND	↓(77 %)	↑(19 %)	Soyinka et al. (2010)
Ritonavir	Healthy volunteers	Open label Prospective Cross over	10	600 mg orally × 1	Steady-state 200 mg orally every 12 h × 9 days	Quinine (3-OH quinine)	↓(90 %)	↓59 %)	ND	↔	ND	ND	ND	Soyinka et al. (2010)
Lopinavir/ Ritonavir	Healthy volunteers Age: 18–55 years	Open label Prospective Cross over	12	648 mg orally × 1	Steady-state 400/100 (lopinavir/ ritonavir) orally twice daily for 12 days	Quinine	↓(36 %) *free values	↓(33 %)	ND	↔	↑(24 %)	↑(55 %)	↓(20 %)	Nyunt et al. (2012)
Lopinavir/ Ritonavir	Healthy volunteers Age: 18–55 years	Open label Prospective Cross over	12	648 mg orally × 1	Steady-state 400/100 (lopinavir/ ritonavir) orally twice daily for 12 days	Quinine (3-OH quinine)	↓(65 %) *free values	↓(59 %)	ND	↔	↑(103 %)	↑(185 %)	↓(29 %)	Nyunt et al. (2012)

AUC area under the plasma concentration-time curve, *CL/F* apparent oral clearance, *Cmax* maximal concentration, *Cmin* minimal concentration, *M* male, *ND* data not available, *t1/2* half-life, *PK* pharmacokinetics, *Tmax* time to reach maximum concentration, *Vd/F* apparent volume of distribution, *Wt* weight, ↔ no significant change

by CYP3A4 (German and Aweeka 2008), dihydroartemisinin is primarily conjugated by uridine 5′-diphospho-(UDP)-glucuronosyltransferase UGT1A9 and UGT2B7 (Ilett et al. 2002), and rifampin is known to induce most of these enzymes. The marked reductions in AUC and Cmax of artemether, lumefantrine, and dihydroartemisinin suggest the possibility of significantly decreased efficacy, which was not tested in this malaria-free patient population but certainly warrants avoidance of the combination.

Lefevre et al. (2002) studied the effects of ketoconazole (400 mg orally × 1, then 200 mg orally daily for 4 days) on the pharmacokinetics of a single dose of artemether/lumefantrine (80/480 mg orally) in healthy subjects (n = 16) using an open label, prospective, randomized, cross over study. Ketoconazole significantly increased the AUC_{∞} (740 ± 286 vs. 320 ± 138 ng h/mL, mean ± SD), Cmax (225 ± 77 vs. 104 ± 40 ng/mL), and t1/2 (2.5 ± 1.1 vs. 1.9 ± 0.8 h), but had little effect on the Tmax of artemether when given in combination compared to artemether/lumefantrine alone, respectively. Similarly, ketoconazole significantly increased the AUC_{∞} (501 ± 155 vs. 331 ± 111 ng h/mL) and Cmax (142 ± 55 vs. 104 ± 45 ng/mL), but had insignificant effects on Tmax and t1/2 of dihydroartemisinin. On the other hand, ketoconazole only significantly increased the AUC_{∞} (333 ± 194 vs. 207 ± 123 μg h/mL) of lumefantrine, but had little effect on the other pharmacokinetic parameters. Ketoconazole is a known inhibitor of CYP3A4, and these findings support an inhibitory effect on the intestinal and/or hepatic metabolism of artemether and lumefantrine, which are both metabolized predominately by CYP3A4 (German and Aweeka 2008) in humans. However, the apparent increase in dihydroartemisinin exposure, which is primarily conjugated by UGT enzymes (Ilett et al. 2002), may be explained by other minor CYP450 pathways of artemether metabolism that may have played more prominent roles in the presence of a CYP3A4 inhibitor (i.e. increased artemether in the presence of ketoconazole resulted in more metabolism through these alternative pathways that resulted in increased dihydroartemisinin formation). Nevertheless, increased exposure of artemether, dihydroartemisinin, and lumefantrine did not correspond with increased QTc prolongation in these healthy volunteers, suggesting little clinical correlation from these pharmacokinetic perturbations. These findings remain to be determined in clinically relevant conditions (i.e. steady state) in the diseased population.

4.3 Effects of HIV-Antiviral Drugs on the Pharmacokinetics of Artemisinin Derivatives

Readers are referred to a detailed review on this subject (8 primary articles on 44 interactions) already published (in a similar format as that used in this book) in *Clinical Pharmacokinetics* (Kiang et al. 2014).

4.4 Effects of Drugs on the Pharmacokinetics of Atovaquone

In a study enrolling six volunteers with HIV infection, Falloon et al. (1999) examined the effects of steady-state trimethoprim-sulfamethoxazole (160/800 mg orally every 12 h) on the pharmacokinetics of steady-state atovaquone (500 mg orally) using an open label, prospective, cross over design. The major finding was that trimethoprim-sulfamethoxazole did not affect the average concentration of atovaquone (9.2 ± 3.2 μg/mL alone vs. 9.2 ± 5.4 μg/mL combination, mean ± SEM), but other pharmacokinetic parameters such as Cmax, AUC, minimum concentration (Cmin), Tmax, t1/2 were not reported. These findings are consistent with the lack of in vitro data supporting this particular interaction, but the data reported in this study should be interpreted in the context of a small sample size.

Using an open label, prospective design, van Luin et al. (2010) studied the effects of steady-state efavirenz (600 mg, n = 20), lopinair/ritonavir (400/100 mg, n = 19), or atazanavir/ritonavir (300/100 mg, n = 19) in HIV-infected individuals taking a single, prophylactic dose of atovaquone/proguanil (250/100 mg) compared to healthy volunteers (n = 18) receiving single doses of the combination antimalarial alone. No absolute numerical values of pharmacokinetic parameters were reported, but the authors indicated significant reductions in the AUC of atovaquone (as determined by AUC ratio between combination group vs. healthy control) for HIV patients receiving efavirenz (0.25 [0.16–0.38], ratio [95 % CI]), lopinavir/ritonavir (0.26 [0.17–0.41]), and atazanavir/ritonavir (0.54 [0.35–0.41]). Similar reductions in Cmax ratios for atovaquone were also observed from efavirenz (0.56 [0.39–0.82], ratio [95 % CI]), lopinavir/ritonavir (0.56 [0.39–0.82]), and atazanavir/ritonavir (0.51 [0.36–0.73]), respectively. Although atovaquone undergoes minimal oxidation, it is extensively conjugated and undergoes significant enterohepatic recirculation. Efavirenz, postulated to have an inductive effect on phase II conjugation enzymes, is a known agonist of the constitutive androstane receptor and the pregnane X receptor that can possibly modulate UGT enzymes responsible for the conjugation of atovaquone (Faucette et al. 2007). Likewise, ritonavir can have inductive effects toward UGT isoenzymes (Foisy et al. 2008), but further reaction phenotyping studies are needed to characterize whether ritonavir has an effect on the UGT enzymes responsible for conjugation of atovaquone. However, the findings from this study should be interpreted in the context of an unmatched baseline (i.e. differences between age, disease state, different proportion of sex, etc.) between the two comparator groups. The effects of the observed drug interaction reported in this study under steady-state dosing conditions also remain to be determined.

4.5 Effects of Drugs on the Pharmacokinetics of Chloroquine

Ette et al. (1987a) studied the effects of single-dose cimetidine (400 mg orally) on the pharmacokinetics of single-dose chloroquine (600 mg orally) in healthy male volunteers using an open label, randomized, design with parallel control (n = 5 in each group). Cimetidine significantly increased the t1/2 (4.62 ± 0.70 vs. 3.11 ± 0.50 days, mean ± SD), volume of distribution (0.72 ± 0.10 vs. 0.46 ± 0.07 L/kg), and decreased Cl/F (0.23 ± 0.02 vs. 0.49 ± 0.04 L/kg/day) of chloroquine in the combination group compared to the control, respectively. Cimetidine also affected the pharmacokinetics of the metabolite, monodesethylchloroquine, where a significant reduction in AUC_{last} (2.24 ± 0.97 vs. 4.23 ± 1.49 μg d/ml, mean ± SD) and cumulative amount of the metabolite excreted into the urine in 7 days (19.23 ± 2.54 vs. 33.72 ± 6.34 μg) was observed for the treatment compared to the control, respectively. No effects on Cmax or Tmax of the metabolite were reported and no other pharmacokinetic parameters for either the parent or metabolite was reported. These data, suggesting that cimetidine reduced the metabolic conversion of chloroquine to its metabolite, are supported by currently known metabolic characteristic of both drugs, that chloroquine is primarily metabolized by CYP3A4 (Kim et al. 2003; Projean et al. 2003) and CYP2D6 (Projean et al. 2003) and cimetidine is a known inhibitor of these CYP450 isoenzymes (Madeira et al. 2004; Martinez et al. 1999).

To follow up with the interaction study between cimetidine and chloroquine, Ette et al. (1987b) examined the effects of an alternative H2 blocker, ranitidine, on the pharmacokinetics of chloroquine in healthy male volunteers using an open label, randomized, design with parallel control (n = 5 in each group). In contrast to cimetidine, ranitidine did not affect the pharmacokinetics of chloroquine, as evident by comparable AUC_{∞} (11.12 ± 2.55 vs. 9.04 ± 1.01 μgd/mL, mean ± SD), rate of drug elimination (0.19 ± 0.01 vs. 0.21 ± 0.02 day^{-1}), Cl/F (28.30 ± 7.20 vs. 33.50 ± 3.63 L/day), and Vd/F (146.14 ± 27.30 vs. 156.67 ± 0.67 L) for the combination group compared to the control, respectively. The disposition of the chloroquine metabolite was not determined, and no other pharmacokinetic parameters were reported in this study. The lack of pharmacokinetic interaction between ranitidine and chloroquine is supported by the minimal inhibitory effects of ranitidine toward CYP2D6 and CYP3A4 (Martinez et al. 1999), which are both known to metabolize chloroquine in humans (Kim et al. 2003; Projean et al. 2003). However, these negative findings should be interpreted in the context of the small sample size and the lack of an a priori power analysis.

Onyeji et al. (1993) studied the effects of single-dose imipramine (50 mg) on the pharmacokinetics of single-dose chloroquine (300 mg) in healthy volunteers using an open label, prospective, randomized cross over design. The major finding was that imipramine did not affect the pharmacokinetics of chloroquine or its metabolite, desethylchloroquine, as evident by comparable Cmax (140 ± 18.6 vs. 146.7 ± 10 ng/mL, mean ± SD), Tmax (3.7 ± 1.5 vs. 3.0 ± 1.7 h), t1/2

(165.9 ± 24.3 vs. 163.0 ± 31.3 h), Cl/F (0.588 ± 0.088 vs. 0.605 ± 0.1 L/h/kg), and Vd/F (140.5 ± 30.4 vs. 148.3 ± 36.9 L/kg), for combination treatment compared to chloroquine alone, respectively. Likewise, little effect of imipramine on the pharmacokinetics of desethylchloroquine was observed as evident by comparable AUC_{last} (4,883 ± 984 vs. 5,103 ± 1,888 ng h/mL, mean ± SD) and the mean percentage of the metabolite excreted in the urine (2.70 ± 0.29 vs. 2.78 ± 0.41 %), for the combination compared to the control, respectively. Since both imipramine/desipramine and chloroquine are substrates of CYP2D6 (Projean et al. 2003; Ereshefsky et al. 1995), there exists a potential for competitive type drug-drug interactions, whereby imipramine or desipramine would displace chloroquine from enzyme binding sites, an effect not observed in this in vivo study. These negative findings, however, should be interpreted in the context of the sample size (n = 6).

Raina et al. (1993) studied the effects of single oral doses of aspirin (325 mg), acetaminophen (500 mg), and analgin (500 mg) on the pharmacokinetics of a single oral dose of chloroquine (600 mg) in healthy male volunteers (n = 8) using a prospective, open label, cross over design. Aspirin did not alter the absorption t1/2 (0.98 ± 0.07 vs. 1.01 ± 0.08 h, mean ± SEM), Cmax (65.5 ± 2.2 vs. 67.7 ± 2.6 μg/L), t1/2 (162.8 ± 13.3 vs. 161.7 ± 15.2 h), or AUC_{∞} (10.02 ± 0.1 vs. 9.93 ± 0.1 μg/μL/h) in combination treatment compared to chloroquine alone, respectively. On the other hand, acetaminophen significantly increased the Cmax (79.2 ± 3.2 vs. 67.7 ± 2.6 μg/L) and AUC_{∞} (12.3 ± 0.9 vs. 9.93 ± 0.1 μg h/μL) but had little effect on absorption t1/2 (0.92 ± 0.05 vs. 1.01 ± 0.08 h) and elimination t1/2 (179.2 ± 1.3 vs. 161.7 ± 15.2 h) co-administered with chloroquine compared to chloroquine alone, respectively. A similar pattern of interaction was also observed with analgin, where increased Cmax (82.0 ± 3.3 vs. 67.7 ± 2.6 μg/L) and AUC_{∞} (12.2 ± 0.9 vs. 9.93 ± 0.1 μg h/μL) of chloroquine were accompanied with little changes in absorption t1/2 (0.95 ± 0.6 vs. 1.01 ± 0.08 h) and elimination t1/2 (188.3 ± 18.5 vs. 161.7 ± 15.2 h) in combination treatment compared to chloroqine alone, respectively. Since the metabolism of aspirin does not involve CYP450 enzymes, and it is not a significant inhibitor of the enzyme system, there lacked a mechanism for a drug interaction with chloroquine. Acetaminophen is a substrate of CYP2D6 and CYP3A4 (Dong et al. 2000; Laine et al. 2009) and thus is potentially a competitive inhibitor of chloroquine. On the other hand, little is known of the metabolism properties of analgin making it difficult to hypothesize the nature of its interaction with chloroquine. The clinical relevance of these effects, however, remain unknown since the magnitude of the pharmacokinetics interactions are fairly small and should be studied in the true patient population.

Rengelshausen et al. (2004) determined the effects of methylene blue (130 mg orally twice daily × 3 days) on the pharmacokinetics of chloroquine (2.5 g or 1.875 g orally given over 3 days) and hydroxychloroquine in 24 healthy volunteers using a randomized, open label, placebo controlled, parallel group design. The combination of methylene blue and chloroquine did not affect the AUC_{∞} (249 ± 98.2 vs. 315 ± 65.0 μg h/L/kg, mean ± SD, combination vs. control) or the t1/2 (154 ± 28.9 vs. 162 ± 17.3 h) of chloroquine in whole blood. On the other

hand, although methylene blue did not affect the t1/2 (241 ± 35.6 vs. 258 ± 24.7 h), it significantly reduced the AUC_{∞} (104 ± 40.3 vs. 159 ± 66.6 μg h/L/kg) of desethylchloroquine. The renal clearance of chloroquine was similar in the combination group (336 ± 130 mL/min) compared to the control (316 ± 178 mL/min). These results suggest that methylene blue did not have a significant impact on the pharmacokinetics of chloroquine, which is supported by the lack of any known mechanistic basis (i.e. drug metabolism interaction) between methylene blue and chloroquine. It is not known if the significant but modest reduction of desethylchloroquine is of any clinical relevance, but the potential mechanism (i.e. enhanced clearance or reduced production) should be further investigated in patients under steady-state conditions.

Cook et al. (2006) studied the effects of azithromycin (given as 3 g orally divided over 3 days) on the pharmacokinetics of chloroquine (given as 2.5 g orally divided over 3 days) in healthy volunteers using an open label, prospective, randomized, parallel group design (n = 24 vs. 15 in the control group). Azithromycin did not affect the weight-adjusted Cmax (15.6 vs. 16.5 kg μg/mL, mean), Tmax (6.08 vs. 6.60 hs), AUC_{∞} (1,626 vs. 1,690 kg μg h/mL) or t1/2 (185 vs, 206 h) of chloroquine, when given in combination compared to chloroquine alone, respectively. Likewise, azithromycin did not affect the weight-adjusted Cmax (4.57 vs. 4.99 kg μg/mL, mean), Tmax (6.79 vs. 13.2 hs), AUC_{∞} (726 vs. 761 kg μg h/mL) and t1/2 (239 vs. 247 h) of the major metabolite, desethlchloroquine, when given in combination compared to chloroquine alone, respectively. No other pharmacokinetic parameters were reported in this study. These observations are supported by the fact that azithromycin lacks inhibitory effects on the CYP450 isoenzymes known to catalyze chloroquine in humans (Kim et al. 2003; Projean et al. 2003). The findings from this study, however, should be interpreted in the context of an unmatched baseline between the study and control groups (i.e. significant weight difference and sample sizes).

Gbotosho et al. (2008) examined the effects of promethazine (25 mg orally × 1, then 12.5 mg orally Q8H for 5 days) or chlorpheniramine (8 mg orally × 1, then 4 mg orally Q8H for 7 days) on the pharmacokinetics of chloroquine (10 mg/kg orally × 1 dose, followed by 5 mg/kg orally daily for 2 days) in healthy volunteers (n = 5) using a prospective, open label, parallel group design. Despite trends toward differences, promethazine did not affect the Cmax (442.8 ± 230.44 vs. 442.9 ± 40.50 ng/mL, mean ± SD), Tmax (4.3 ± 2.44 vs. 2.5 ± 0.86 h), t1/2 (71.5 ± 24.19 vs. 93.6 ± 54.60 h), and AUC (30,903 ± 8,315 vs. 31,555 ± 7,234 ng h/mL) of chloroquine in plasma for the combination treatment compared to chloroquine given alone, respectively. Likewise, only trends toward differences were observed for the effects of chlorpheniramine on the Cmax (341.1 ± 149.0 vs. 442.9 ± 40.50 ng/mL, mean ± SD), Tmax (6.5 ± 3.54 vs. 2.5 ± 0.86 h), t1/2 (101.1 ± 41.38 vs. 93.6 ± 54.60 h), and AUC (24,857 ± 5,631 vs. 31,555 ± 7,234 ng h/mL) of chloroquine in plasma, respectively. A similar pattern was also observed in erythrocytes, where promethazine had insignificant effects on the pharmacokinetics of chloroquine. On the other hand, chlorpheniramine significantly increased the Cmax (2492.7 ± 817.38

vs. 2008.9 ± 700.50 ng/mL, mean ± SD) and AUC (214516.3 ± 5631.12 vs. 99921.2 ± 77389.2 ng h/mL) of chloroquine in erythrocytes, when given in combination compared to chloroquine alone, respectively. No other pharmacokinetic parameters were reported in the study. Although the mechanism of the interaction between chlorpheniramine and chloroquine remains to be clarified, the authors suggested that chlorpheniramine enhances chloroquine concentrations in erythrocytes by the inhibition of transport enzymes. The data from this study, however, should be interpreted in the context with small sample size (and the large variability observed.

4.6 Effects of Drugs on the Pharmacokinetics of Mefloquine

Na-Bangchang et al. (1991) studied the effects of metoclopramide (single oral dose of 10 mg) on the pharmacokinetics of mefloquine (single oral dose of 750 mg) in healthy male volunteers (n = 7) using an open label, prospective, cross over design. Metoclopramide significantly decreased the absorption t1/2 (2.4 ± 0.8 vs. 3.2 ± 0.6 h, mean ± SD) increased the Cmax (1,570 ± 403 vs. 1,196 ± 218 ng/mL), but had no effects on the AUC_{∞} (21.3 ± 5.4 vs. 19.9 ± 3.9 μgd/mL) or t1/2 (17.5 ± 2.3 vs. 19.2 ± 3.5 days) of mefloquine when given in combination compared to mefloquine alone, respectively. These findings suggest that metoclopramide had an effect on the absorption but not the intrinsic clearance of mefloquine in these healthy volunteers. These data are supported by the lack of a molecular basis for a metabolic drug interaction between this drug pair.

Karbwang et al. (1991) examined the effect of steady-state ampicillin (250 mg orally 4 times daily for 5 days) on the disposition of mefloquine (750 mg orally × 1) in healthy male Thai volunteers (n = 8) via an open label, prospective, cross over study. Steady-state ampicillin increased the Cmax (1,648 ± 509 vs. 1,228 ± 223 ng/mL, mean ± SD), decreased the t1/2 (15.3 ± 3.31 vs. 17.7 ± 2.51 days) and Vd/F (14.1 ± 6.60 vs. 19.4 ± 3.03 L/kg), but did not affect the Tmax (9 ± 2 vs. 6 ± 3 h), AUC_{∞} (21.5 ± 8.74 vs. 18.6 ± 2.14 μgd/mL) or CL/F (0.523 ± 0.229 vs. 0.529 ± 0.079 mL/min/kg) of mefloquine when given in combination compared to mefloquine alone, respectively. The decreased mefloquine t1/2 in the presence of ampicillin was proposed by the authors to be due to decreased volume of distribution, which may have been the result of decreased tissue binding and not an induction of intrinsic clearance of mefloquine, since total exposure remained the same. This is consistent with the lack of a known molecular basis for drug interaction at the metabolism enzymatic level between this drug pair. However, it is unclear why ampicillin significantly increases the Cmax of mefloquine. The proposed mechanism of altered enterohepatic recirculation is complex and warrants further investigation.

Karbwang et al. (1992) also examined the effects of tetracycline (250 mg orally 4 times daily for 7 days) on the disposition of a single dose of mefloquine in healthy male Thai volunteers (n = 11 vs. 9 in control group) using a prospective, open label, randomized, parallel group design. Steady-state tetracycline increased the Cmax (1,598 ± 630 vs. 1,155 ± 184 ng/mL, mean ± SD), decreased the t1/2 (14.4 ± 6.2 vs. 19.3 ± 2.9 days) and Vd/F (13.3 ± 4.4 vs. 19.9 ± 4.4 L/kg), but did not affect the Tmax (8.2 ± 4.2 vs. 5.7 ± 2.5 h), AUC_{∞} (22.2 ± 13.5 vs. 19.3 ± 2.9 μg d/mL) or CL/F (0.535 ± 0.239 vs. 0.502 ± 0.105 mL/min/kg) of mefloquine when given in combination compared to mefloquine alone, respectively. The same pattern of perturbation was also observed on the pharmacokinetics of mefloquine from the coadministration of ampicillin (Karbwang et al. 1991). The authors hypothesized, for both studies, that an effect on enterohepatic recircuation by these antibiotics and a displacement in tissue binding may be possible mechanisms for these observations. However, unlike ampicillin, tetracycline can have an inhibitory effect toward CYP3A4, the principal enzyme responsible for the metabolism of mefloquine (Fontaine et al. 2000); therefore, decreased intrinsic clearance may play an additional role in the interaction between tetracycline and mefloquine. However, as in the case for ampicillin (Karbwang et al. 1991), all of these proposed mechanisms require further confirmation.

Kolawole et al. (2000) studied the effects of cimetidine (400 mg orally twice daily for 3 days) on the disposition of mefloquine (500 mg orally × 1) in healthy male volunteers (n = 6) and patients diagnosed with peptic ulcers (n = 6) using an open label, prospective, cross over design. In healthy male volunteers, cimetidine significantly increased the Cmax (2.52 ± 0.27 vs. 1.77 ± 0.23 μg/mL, mean ± SD) and AUC_{∞} (26.20 ± 18.90 vs. 19.05 ± 7.01 mg day/L), but had little effect on absorption t1/2 (2.70 ± 1.59 vs. 4.20 ± 3.15 h), elimination t1/2 (20.38 ± 6.34 vs. 18.56 ± 9.79 days), Tmax (6.50 ± 4.00 vs. 8.00 ± 3.10 h), Vd/F (11.60 ± 6.66 vs. 9.43 ± 3.77 L/kg), and Cl/F (0.391 ± 0.18 vs. 0.453 ± 0.151 L/day/kg) of mefloquine when given in combination compared to mefloquine alone, respectively. Similar findings were obtained in patients diagnosed with peptic ulcer, where cimetidine significantly increased the Cmax (2.41 ± 0.10 vs. 2.00 ± 0.30 μg/mL, mean ± SD) and AUC_{∞} (26.24 ± 9.81 vs. 19.85 ± 9.48 mg day/L), but had little effect on absorption t1/2 (1.7 ± 0.3 vs. 1.9 ± 1.0 h), elimination t1/2 (19.40 ± 3.30 vs. 18.70 ± 7.12 days), Tmax (7.0 ± 1.7 vs. 7.5 ± 3.0 h), Vd/F (8.50 ± 2.30 vs. 11.12 ± 4.04 L/kg), and Cl/F (0.315 ± 0.10 vs. 0.454 ± 0.19 L/day/kg) of mefloquine when given in combination compared to mefloquine alone, respectively. Although the small sample size and the large variability precluded the establishment of statistical significance for some pharmacokinetics parameters (i.e. clearance and t1/2), these findings support the known inhibitory effects of cimetidine toward CYP3A4 (Martinez et al. 1999), the principal enzyme responsible for the metabolism of mefloquine in humans (Fontaine et al. 2000). Because the magnitude of the interaction is small, however, it is unclear if the interaction is translated to clinically significant effects.

Ridtitid et al. (2000) examined the effects of rifampin (steady-state dosing of 600 mg orally daily for 7 days followed by twice weekly for total of 56 days) on the

pharmacokinetics of a single oral dose of mefloquine (500 mg) in healthy Thai males (n = 7) using an open label, prospective, cross over design. Rifampin significantly decreased the Cmax (695.7 ± 56.6 vs. 855.6 ± 168.0 ng/mL, mean ± SD), t1/2 (113.4 ± 49.7 vs. 305.5 ± 47.2 h) and AUC_{∞} (119.8 ± 54.9 vs. 373.7 ± 57.5 mg h/L), increased Cl/F (0.08 ± 0.03 vs. 0.021 ± 0.004 L/h/kg) but had little effect on Tmax (8.7 ± 3.9 vs. 8.2 ± 2.9 h) of mefloquine when given together compared to mefloquine alone, respectively. The authors also measured the concentrations of the major carboxylic acid metabolite and found that cimetidine significantly increased the Cmax (1194.5 ± 249.1 vs. 813.2 ± 298.0 ng/mL), decreased Tmax (52.5 ± 28.8 vs. 220.6 ± 69.8 h) and t1/2 (307.5 ± 28.8 vs. 506.7 ± 127.6 h), but had little effect on the AUC_{∞} and CL/F of the mefloquine metabolite when given in combination compared to mefloquine alone, respectively. These findings are consistent with the known strong inductive effects of rifampin toward CYP3A4, the principal enzyme responsible for the metabolism of mefloquine in humans (Fontaine et al. 2000). Given the magnitude of the pharmacokinetic interaction, it is advised that concomitant administration of rifampin and mefloquine should be avoided.

Ridtitid et al. (2005) examined the effects of ketoconazole (400 mg orally daily for 10 days) on the pharmacokinetics of a single oral dose of mefloquine (500 mg) in healthy male Thai volunteers (n = 8) using a prospective, open label, cross over design. Steady-state ketoconazole significantly increased the AUC_{last} (286.05 ± 64.25 vs. 159.66 ± 33.28 mg h/L, mean ± SD), t1/2 (448.41 ± 103.88 vs. 322.68 ± 99.95 h) and Cmax (567.65 ± 88.69 vs. 345.10 ± 43.22 ng/mL), but had little effect on Tmax (12.36 ± 3.00 vs. 17.99 ± 8.17 h) of mefloquine when given in combination compared to mefloquine alone, respectively. Ketoconazole also decreased the AUC_{last} (352.29 ± 47.08 vs. 492.43 ± 141.66 mg h/L) and Cmax (419.65 ± 45.02 vs. 606.11 ± 184.00 ng/mL) of the carboxylic acid metabolite of mefloquine in these healthy volunteers. These results are supported by the known inhibitory effects of ketoconazole toward CYP3A4, the principal enzyme responsible for the metabolism of mefloquine in humans (Fontaine et al. 2000). These data, in conjunction with those of Kolawole et al. (2000) using cimetidine and Ridtitid et al. (2000) using rifampin, strongly suggest a role of CYP3A4 in mediating the drug-drug interaction associated with mefloquine. With respect to ketoconazole, the extent of interaction would warrant dosage adjustment and, ideally, avoidance of concurrent administration of the drug pair.

Khaliq et al. (2001) examined the effects of steady-state ritonavir (200 mg orally twice daily for 7 days) on the pharmacokinetics of mefloquine (250 mg orally daily for 3 days, then once weekly for 4 weeks) in healthy volunteers (n = 12) using an open label, prospective, cross over design. Ritonavir did not affect the AUC_{last} (140 ± 26.7 vs. 144 ± 30.7 μg h/mL, mean ± SD), Cmax (3,463 ± 1,842 vs. 5,063 ± 2,468 ng/mL), t1/2 (3.1 ± 0.8 vs. 3.1 ± 0.7 h), Cl/F (299 ± 146 vs. 146 ± 76.1 mL/min), Tmax (4.0 vs. 4.0 h, mean), and fraction unbound (0.43 ± 0.19 vs. 0.45 ± 0.15) of mefloquine when given in combination compared to mefloquine alone, respectively, despite having a significant inhibitory effect on in vivo CYP3A4 activity as measured by the erythromycin breath test. Little effects

by steady-state ritonavir on the pharmacokinetics of (+)-RS mefloquine, (−)-SR mefloquine and the carboxylic acid metabolite of mefloquine were observed (i.e. similar AUC, Cmax, Cl/F values). Likewise, the metabolite to mefloquine ratio also remained unchanged (1.81 ± 0.76 vs. 1.85 ± 0.94). Although one can argue that the erythromycin breath test may not be selective toward CYP3A4 activity, the lack of inhibitory effects of ritonavir on the metabolism of mefloquine is in contradiction to the known metabolic properties of these agents: that CYP3A4 is the principal enzyme responsible for the metabolism of mefloquine in humans (Fontaine et al. 2000) and ritonavir is a potent inhibitor of this isoenzyme (Ernest et al. 2005). These negative results should be interpreted in the context of the small sample size and large variability, but may also suggest that other metabolic or pharmacokinetic processes or interactions may have taken place to counteract the effects of the CYP3A4-mediated interaction.

4.7 Effects of Drugs on the Pharmacokinetics of Proguanil

van Luin et al. (2010), using an open label, prospective design, studied the effects of steady-state efavirenz (600 mg, n = 20), lopinair/ritonavir (400/100 mg, n = 19), or atazanavir/ritonavir (300/100 mg, n = 19) in HIV-infected individuals taking a single, prophylactic dose of atovaquone/proguanil (250/100 mg) compared to healthy volunteers (n = 18) receiving single doses of the combination antimalarial alone. No absolute numerical values of pharmacokinetic parameters were reported, but the authors indicated significant reductions in the AUC of proguanil (as determined by AUC ratio between combination group vs. healthy control) for HIV patients receiving efavirenz (0.57 [0.35–0.93], ratio [95 % CI]), lopinavir/ritonavir (0.62 [0.39–0.99]), and atazanavir/ritonavir (0.59 [0.38–0.93]), which are in contrast to a lack of effect on Cmax ratios. Because proguanil can be metabolized by CYP3A (Birkett et al. 1994), CYP2C19 (Coller et al. 1999) and CYP1A2 (Coller et al. 1999), these effects may possibly be explained by the known inductive effects of efavirenz toward CYP3A isoenzymes (Hariparsad et al. 2004) or the inductive effects of lopinavir or ritonavir toward CYP2C19 and CYP1A2 isoenzymes (Yeh et al. 2006). However, further mechanistic studies (i.e. in an in vitro system) are needed to definitively confirm these hypotheses, and the findings from this study should also be interpreted in the context of an unbalanced comparator group (i.e. healthy vs. HIV-infected patients) and dosing the antimalarial drug in a non-steady-state fashion.

Soyinka and Onyeji (2010) studied the effects of efavirenz (400 mg orally daily for 11 days) on the pharmacokinetics of a single oral dose of proguanil (300 mg) in healthy volunteers (n = 15), using an open label, prospective cross over study. In contrast to the effects observed by van Luin et al. (2010), efavirenz significantly increased the Tmax (4.80 [4–8] vs. 2.8 [2–4] h, median [range]), Cmax (3.75 ± 0.48 vs. 2.55 ± 0.24 mg/L), t1/2 (23.24 ± 4.08 vs. 16.50 ± 4.55 h), AUC (97.00 ± 23.33 vs. 45.58 ± 12.75 mg h/L), and decreased the Cl/F (3.25 ± 0.73 vs. 7.08 ± 1.97 L/h)

of proguanil, when given in combination compared to proguanil alone, respectively. Corresponding changes in the pharmacokinetics of cycloguanil were also observed, as evident by decreased Tmax (8.21 [6–12] vs. 6.67 [4–8] h, median [range]), Cmax (0.42 ± 0.09 vs. 0.61 ± 0.13 mg/L), and AUC (10.25 ± 4.44 vs. 16.19 ± 6.01 mg h/L) for the combination compared to proguanil alone, respectively. These results suggest that efavirenz inhibited the bioactivation of proguanil into cycloguanil, in a reaction presumably mediated by the inhibition of CYP2C19 (von Moltke et al. 2001), the principal enzyme responsible for the bioactivation of proguanil (Funck-Brentano et al. 1997). The discrepancies observed between van Luin et al. (2010) which showed a decrease of proguanil AUC in the presence of efavirenz, and the current study, remain to be clarified. One might hypothesize that the differences may be due to study design (e.g. the van Luin study conducted the comparison between healthy volunteers and HIV-infected individuals) or experimental conditions (e.g. the van Luin study used the combination atovaquone/proguanil) which could have generated confounding factors affecting the observation. Further mechanistic studies (i.e. using a model such as human hepatocytes that can be subjected to induction and inhibition modulations) are needed to clarify relative contributions of the inductive (i.e. toward CYP3A4) vs. inhibitory (i.e. toward CYP2C19) effects of efavirez on the bioactivation of proguanil.

The effects of omeprazole (40 mg orally daily for 7 days) on the pharmacokinetics of proguanil (200 mg orally as a single dose) was reported by Funck-Brentano et al. (1997) in healthy subjects ($n = 12$) via an open label, prospective, cross over design. Steady-state omeprazole decreased the t1/2 (19 ± 3 vs. 15 ± 3 h, mean $\pm$ SD), Cl/F (70 ± 16 vs. 103 ± 22 L/h), partial metabolic clearance (of proguanil to cycloguanil, the major active metabolite) (8 ± 3 vs. 23 ± 8 L/h), and increased the AUC ($2{,}634 \pm 616$ vs. $1{,}767 \pm 386$ ng h/mL) of proguanil, when given in combination compared to proguanil alone, respectively. These observations were corresponded with significantly decreased cycloguanil AUC (589 ± 161 vs. $1{,}107 \pm 222$ mg h/mL) in the presence of omeprazole. Concurrent in vitro investigation using human liver microsomes and CYP450 isoenzyme selective inhibitors in the same study indicated that omeprazole reduced the bioactivation of proguanil to cycloguanil by inhibiting the catalytic activity of CYP2C19, and this was hypothesized to be the mechanism leading to the pharmacokinetic interaction observed in vivo. The reduced bioactivation of proguanil to cycloguanil, in the presence of a CYP2C19 inhibitor such as omeprazole, may potentially lead to decreased therapeutic efficacy, although the clinical relevance of such interactions remains to be determined in patients.

The effects of cimetidine (400 mg orally twice daily for 5 doses) on the pharmacokinetics of proguanil (a single oral dose of 200 mg orally) and cycloguanil were studied by Kolawole et al. (1999) in healthy volunteers ($n = 6$) and patients with peptic ulcer disease ($n = 4$) in an open label, prospective, cross over study. In healthy volunteers, cimetidine significantly increased the Cmax (393.4 ± 104 vs. 208.3 ± 30.3 ng/mL, mean $\pm$ SD), AUC_{∞} ($8{,}991 \pm 2{,}101$ vs. $4{,}670 \pm 1{,}049$ ng h/mL), and t1/2 (22.55 ± 4.19 vs. 15.27 ± 3.73 h), but had little effects on Tmax (3.0 ± 1.6 vs. 3.3 ± 1.4 h), Vd/F (10.74 ± 3.37

vs. 14.00 ± 5.04 L/kg), and Cl/F (5.47 ± 1.14 vs. 10.51 ± 2.17 mL/min/kg) of proguanil, when given in combination compared to proguanil alone, respectively. A similar pattern was observed for patients with peptic ulcer disease, where cimetidine significantly increased the AUC_{∞} (12,155 ± 2,127 vs. 8,261 ± 1,198 ng h/mL), and t1/2 (23.06 ± 8.17 vs. 14.22 ± 2.75 h), but had little effects on Cmax (481.45 ± 69.80 vs. 347.1 ± 54.0 ng/mL, mean ± SD), Tmax (5.3 ± 1.5 vs. 4.5 ± 1.7 h), Vd/F (7.94 ± 2.22 vs. 7.30 ± 1.09 L/kg), and Cl/F (4.11 ± 0.68 vs. 6.00 ± 0.74 mL/min/kg) of proguanil, when given in combination compared to proguanil alone, respectively. In healthy volunteers, cimetidine significantly decreased the Cmax (5.73 ± 3.3 vs. 11.25 ± 7.7 ng/mL) of proguanil, an effect observed in the patient cohort (26.1 ± 21 vs. 38.8 ± 1.8 ng/mL) as well. These observations are supported by the fact that cimetidine is known a potent inhibitor of CYP2C19 (Knodell et al. 1991), the enzyme responsible for the bioactivation of proguanil in the formation of cycloguanil (Funck-Brentano et al. 1997). The reduced bioactivation of proguanil to cycloguanil in the presence of cimetidine may potentially lead to decreased therapeutic efficacy.

4.8 Effects of Drugs on the Pharmacokinetics of Quinine

Couet et al. (1991) studied the effects of doxycycline (200 mg orally every 24 h for 3 days) on the disposition of quinine (20 mg/kg infusion × 4 h, then 15 mg/kg infusion over 20 h, then 25 mg/kg/day over 2 more days) in subjects infected with acute falciparum malaria in Africa, using a prospective, open label, parallel group design (n = 13 in each group). Doxycycline did not affect the pharmacokinetics of quinine, as evident by comparable Vd/F (1.44 ± 0.48 vs. 1.32 ± 0.32 L/kg, mean ± SD), Cl/F (0.145 ± 0.085 vs. 0.125 ± 0.047 L/h/kg), and t1/2 (7.79 ± 4.20 vs. 7.99 ± 3.08 h) for the combination group compared to quinine alone, respectively. No other pharmacokinetics parameters were reported by the authors. These negative findings are supported by the lack of a metabolic basis for a drug interaction between this drug pair: based on in vitro experiments, quinine is known to be metabolized primarily by CYP3A4 (Li et al. 2003) and doxycycline is not known to have inhibitory effects toward this particular isoenyzme.

The effects of steady-state estrogen- and progestin-containing oral contraceptives on the pharmacokinetics of a single oral dose of quinine (600 mg) was studied in a cohort of female subjects (n = 7) of Thai ethnicity compared to a parallel group of controls (n = 7) by Wanwimolruk et al. (1991), using an open label, prospective, non-randomized design. Individuals on oral contraceptive pills had comparable quinine Cmax (5.3 ± 1.0 vs. 5.6 ± 0.9 mg/L, mean ± SD), Tmax (12.5 ± 1.9 vs. 11.8 ± 2.7 h), AUC (85.7 ± 24.4 vs. 88.3 ± 32.2 mg h/L), Cl/F (0.133 ± 0.055 vs. 0.125 ± 0.025 L/h/kg), and percentage bound to protein (22.4 ± 6.1 vs. 22.7 ± 6.2 %) compared to controls taking quinine alone. These data suggest a lack of pharmacokinetic interaction between estrogen- and progestin-containing oral contraceptive pills and quinine, but the negative findings should be interpreted

in the context of small sample (n = 7 per group) and wide variability observed. Because of the wide variety of oral contraceptives used by subjects in the study, it was also difficult to ascribe the results to a single estrogen, progestin type or dose. As well, the pharmacokinetic (or lack of) interaction at clinically relevant conditions (e.g. steady-state dosing) still remain to be clarified.

Wanwimolruk et al. (1995) studied the effects of rifampin (600 mg orally daily × 2 weeks) or isoniazid (300 mg orally daily for 1 week) on the disposition of quinine (600 mg single oral dose) in healthy Thai male volunteers (n = 9) using an open label, prospective, randomized, cross over design. Rifampin significantly decreased the Cmax (2.2 ± 1.1 vs. 4.6 ± 1.0 mg/L, mean ± SD), t1/2 (5.5 ± 3.0 vs. 11.1 ± 3.0 h), AUC (11 ± 4 vs. 66 ± 20 mgh/L), increased CL/F (0.87 ± 0.35 vs. 0.14 ± 0.05 L/h/kg), and had little effects on Tmax or percentage unbound of quinine in the combination group compared to the control, respectively. Rifampin also decreased the AUC of the unbound quinine (1.6 ± 0.8 vs. 9.8 ± 3.5 mgh/L) and the percentage of dose excreted into the urine (1.7 ± 1.8 vs. 7.9 ± 6.5 %), but did not change the renal clearance of quinine. On the other hand, isoniazid did not affect the pharmacokinetics of quinine, as evident by comparable Cmax (4.4 ± 1.6 vs. 4.6 ± 1.0 mg/L), Tmax (3.0 vs. 2.5 h, mean), t1/2 (14.2 ± 2.9 vs. 11.1 ± 3.0 h), CL/F (0.16 ± 0.04 vs. 0.14 ± 0.05 L/h/kg), AUC (56 ± 13 vs. 66 ± 20 mgh/L), and the percentage of unbound drug (13.9 ± 2.1 vs. 14.8 ± 1.2 %) when given in combination compared to quinine alone, respectively. These data corresponded with small changes in the AUC unbound, the percentage of dose excreted unchanged in urine, and the renal clearance of quinine. The strong inductive effects of rifampin toward CYP3A4 may explain the pharmacokinetic interaction observed in this study, as quinine is known to be metabolized primarily by CYP3A4 (Li et al. 2003). On the other hand, isoniazid does not induce CYP3A4 to a significant extent, which may have translated to the observation of a lack of pharmacokinetic interaction with quinine. Because of the marked increased in clearance and reduction in exposure of quinine by rifampin, the concurrent administration of these agents should be avoided, and therapy substituted with isoniazid, if possible, to avoid the pharmacokinetic interaction.

In patients diagnosed with uncomplicated falciparum malaria, Pukrittayakamee et al. (2003) studied the effects of steady-state rifampin (15 mg/kg/day orally for 7 days) on the pharmacokinetics of quinine (10 mg/kg orally 3 times daily for 7 days) in male subjects (n = 29 vs. 30 control), using an open label, prospective, randomized, parallel group design. Concurrent administration of rifampin significantly decreased the AUC of quinine from 47.5 compared to 11.7 μg day/mL. The change in exposure was accompanied by significantly reduced Tmax (0.5 vs. 1.5 days, median) but similar Cmax values (10.4 vs. 12.7 μg/mL) when subjects were given the combination compared to quinine alone, respectively. Changes in the pharmacokinetics of the metabolite, 3-OH-quinine, were also observed as evident by significantly increased Cmax (1.61 vs. 1.2 μg/mL) and a shorter Tmax (2 vs. 4.5 days) for the combination compared to quinine alone, respectively. The exposure ratio between quinine and 3-OH quinine was also significantly reduced for subjects receiving rifampin (no value reported in manuscript), supporting an

enhanced intrinsic clearance of quinine by rifampin. These results are consistent with those reported by Wanwimolruk et al. (1995) in healthy male volunteers; rifampin mostly likely increased the metabolic clearance (i.e. by inducing CYP3A4) of quinine in this patient population. Because there was evidence for a significantly reduced cure rate in this study, the drug combination between rifampin and quinine should be avoided to ensure efficacy.

Soyinka et al. (2009) examined the effects of steady-state nevirapine (200 mg every 12 h orally) on the disposition of a single dose of quinine (600 mg orally) in healthy volunteers (n = 14), using an open label, prospective, randomized, cross over design. Nevirapine significantly decreased the Cmax (2.83 ± 0.16 vs. 1.81 ± 0.06 μg/mL, mean ± SD), t1/2 (11.35 ± 0.72 vs. 5.84 ± 0.76 h), AUC_{last} (53.29 ± 4.01 vs. 35.48 ± 2.01 μg h/mL), increased the Cl/F (11.32 ± 0.84 vs. 16.97 ± 0.98 L/h), but had little effects toward Tmax (3.43 vs. 3.57 h) of the combination compared to quinine alone, respectively. These results corresponded with the effects of nevirapine on the pharmacokinetics of the major metabolite of quinine, 3-OH quinine, in that significant increases in Cmax (1.74 ± 0.10 vs. 1.39 ± 0.12 μg/mL), AUC_{last} (56.46 ± 4.41 vs. 43.22 ± 3.68 μg h/mL), and metabolic ratio (1.65 ± 1.01 vs. 0.88 ± 0.10) were observed. The drug interaction may be supported by the known metabolic properties of nevirapine and quinine: that both drugs are primarily metabolized by CYP3A4 (Li et al. 2003; Erickson et al. 1999) and nevirapine is a known inducer of the isoenzyme (Lamson et al. 1999). However, it remains to be studied whether similar pharmacokinetic interactions can be observed between nevirapine and quinine in the patient population under clinical (i.e. steady-state) dosing conditions.

Soyinka et al. (2010) studied the pharmacokinetic interaction between ritonavir (200 mg orally every 12 h for 9 days) and quinine (600 mg single oral dose) in healthy volunteers (n = 10) using an open label, prospective, cross over design. Ritonavir significantly increased the Cmax (10.72 ± 0.32 vs. 2.79 ± 0.22 mg/L, mean ± SD), t1/2 (13.32 ± 0.33 vs. 11.15 ± 0.80 h), AUC_{last} (220.47 ± 6.68 vs. 50.06 ± 4.01 mg h/L), decreased Cl/F (2.71 ± 0.10 vs. 12.01 ± 0.61 L/h), and had little effects on the Tmax of quinine when given in combination compared to quinine alone, respectively. The coadministration of ritonavir also resulted in significantly decreased Cmax (0.96 ± 0.09 vs. 1.80 ± 0.12 mg/L), AUC_{last} (25.61 ± 2.44 vs. 62.80 ± 6.30 mg h/L), and metabolic ratio (0.13 ± 1.01 vs. 1.35 ± 0.10) of 3-hydroxy quinine. The drug interaction may be supported by the known metabolic properties of ritonavir and quinine: that both drugs are primarily metabolized by CYP3A4 (Li et al. 2003; Kumar et al. 1996) and ritonavir is a potent inhibitor of this isoenzyme (Kumar et al. 1996). The marked increase in quinine exposure may require dosage adjustments and monitoring of adverse effects, although the extent and significance of this particular pharmacokinetic interaction should be determined in actual patients under steady-state dosing conditions for quinine.

Nyunt et al. (2012) studied the pharmacokinetic interaction between lopinavir/ritonavir (400/100 mg orally twice daily for 12 days) and a single oral dose of quinine (648 mg) in healthy volunteers (n = 12), using an open label, prospective,

cross over study. The authors measured both total and free drug concentrations and reported similar findings between the two approaches. Based on free drug concentrations, lopinavir boosted by ritonavir significantly decreased the Cmax (0.26 [0.24–0.31] vs. 0.38 [0.36–0.51] mg/L, median [range]), AUC_{last} (3.7 [3.1–4.0] vs. 5.0 [4.4–8.9] mg h/L), t1/2 (8.1 [5.8–9.7] vs. 9.4 [8.4–13.7] h), increased the Vd/F (1,752 [1,513–1,974] vs. 1,345 [1,063–1,655] L) and Cl/F (146 [134–175] vs. 108 [60.4–122] L/h), but had little effect on the Tmax of quinine when given in combination compared to quinine alone, respectively. Similar effects by lopinavir/ritonavir on the disposition of free 3-hydroxyquinine, the major metabolite of quinine, were observed, as evident by decreased Cmax (0.10 [0.08–0.15] vs. 0.24 [0.17–0.29] mg/L, median [range]), AUC_{last} (1.9 [1.1–2.2] vs. 4.3 [3.5–5.1] mg h/L), t1/2 (8.0 [7.5–12.5] vs. 12.6 [10.8–17.6] h), and increased Vd/F (4,995 [3,678–6,167] vs. 2,794 [1,592–3,135] L) or Cl/F (281 [243–483] vs. 125 [105–154] L/h). These findings were also associated with significantly decreased 3-hydroxy quinine to quinine metabolic ratio and increased free fraction of both quinine and 3-hydroxy quinine when lopinavir/ritonavir were given in combination. A significant increase in the free fraction of quinine and its metabolite suggests a protein binding displacement effect by lopinavir/ritonavir which corresponded with the increased Vd/F observed in these volunteers administered the combination. Taken together, these findings seem to suggest an inductive effect of lopinvair/ritonavir toward the metabolism of quinine, which is inconsistent with the data reported by Soyinka et al. (2010). The inconsistencies between the two studies have been attributed by the authors to differences in study design or dosing, which may have had effects on the magnitude of the interaction but should not have resulted in the apparently opposite pharmacokinetic interaction observed between the two studies. Other metabolic pathways affected by lopinavir/ritonavir (i.e. induction of UGT conjugation enzymes or transporters) may also explain the findings reported in this study, but one has to wonder why similar effects were not observed by Soyinka et al. (2010) under comparable experimental conditions. In order to resolve the discrepancies between the two studies, a mechanistic experiment using a model that allows both induction an inhibition modulations (i.e. human hepatocytes) should be carried out.

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Chapter 5
Effects of Antimalarials on the Pharmacokinetics of Co-Administered Drugs

This chapter provides details of studies that describe drug interactions in which antimalarial drugs affect the pharmacokinetics of various co-administered (non-antimalarial) drugs. These antimalarials include amodiaquine, artemether, artemisinin, artesunate, atovaquone, chloroquine, mefloquine, proguanil, and quinine.

5.1 Effects of Amodiaquine on the Pharmacokinetics of Drugs

In order characterize the effects of amodiaquine on CYP450-mediated metabolism in humans, Wennerholm et al. (2006) administered a single dose of amodiaquine (600 mg) in the presence or absence of a single oral dose of a cocktail of CYP450-selective probe substrates: 10 mg debrisoquine (CYP2D6), 20 mg omeprazole (CYP219), 25 mg losartan (CYP2C9), and 100 mg caffeine (CYP1A2) to 12 healthy Swedish subjects who were determined, via genotyping, to be wild-type metabolizers, using a prospective, cross over design where each subject served as their own control. The primary endpoint was the effect of amodiaquine on the metabolic ratios between each probe substrate and a selected metabolite (i.e. debrisoquine/4-hydroxydebrisoquine). However, the typical pharmacokinetic parameters (i.e. AUC, Cmax, t1/2, etc.) were not reported in the study, limiting further mechanistic interpretation of the data. The major finding from the study was that amodiaquine significantly elevated the metabolic ratios for debrisoquine (CYP2D6) and losartan (CYP2C9) by 1.4 and 1.7 fold, respectively, but had little effect on omeprazole and caffeine metabolism. The effects were reversible upon further washout and re-administration of probe substrates alone, supporting the validity of the interaction. The effects of amodiaquine on debrisoquine metabolism in this study is supported by the in vitro finding from Bapiro et al. (2001) where

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amodiaquine was shown to be a strong inhibitor of CYP2D6 activity. Likewise, the lack of effects of amodiaquine on omeprazole and caffeine metabolism is also consistent with its weak inhibitory effects toward their respective isoenzymes (i.e. CYP2C19 and CYP1A2 respectively) in vitro. On the other hand, amodiaquine was shown to be a weak inhibitor, in vitro, of CYP2C9, but had a significant effect on losartan metabolism in this study. The discrepancy, which remains to be clarified, may be due to an effect on alternative metabolic pathways not yet studied for amodiaquine and losartan, or simply the inability to extrapolate in vitro to in vivo findings. A few limitations should be considered while interpreting the findings from this study: although the authors suggested that these effects may be due to amodiaquine and/or its major metabolite N-desethylamodiaquine, the study was actually not designed to determine the relative contribution of either the parent or metabolite toward enzyme inhibition. Also, the dose of amodiaquine used (i.e. 600 mg orally $\times$ 1) is not reflective of the typical clinical approach, where a much higher dose is given at steady-state conditions. The inhibitory effects of amodiaquine may very well be different in these different settings, in the true target population, which remains to be studied (Table 5.1).

5.2 Effects of Artemether on the Pharmacokinetics of Drugs

Asimus et al. (2007) studied the effects (1 and 5 doses) of artemether (50 mg orally) on the metabolic ratios of single oral doses of a CYP450 probe substrate cocktail consisting of caffeine (100 mg), coumarin (5 mg), midazolam (7.5 mg), mephenytoin (100 mg), metoprolol (100 mg), and chlorzoxazone (250 mg) in healthy volunteers (n = 14–15), using a prospective, open label, cross over design. Artemether had little effect on the paraxanthine/caffeine ratio (marker reaction for CYP1A2) in plasma after 1 day (0.83 [0.69–1.02], mean [98.75 % CI]) but decreased the ratio after 5 (0.81 [0.67–0.98]) doses; artemether had little effect on the ratio of 7-OH-coumarin excreted in the urine (marker reaction for CYP2A6) after 1 (1.01 [0.63–1.62]) or 5 days (0.91 [0.57–1.45]); artemether had no effect on the 4-OH-mephenytoin/mephenytoin ratio in plasma (marker reaction for CYP2C19) after 1 (0.95 [0.79–1.14] or 5 (1.20 [1.00–1.44]) days; artemether had no effects on the OH-metoprolol/metoprolol ratio in plasma (marker reaction for CYP2D6) after 1 (0.90 [0.76–1.05] and 5 days (0.97 [0.82–1.13]); artemether had little effect on the 6-OH-chlorzoxzone/chlorzoxazone ratio in plasma (marker reaction for CYP2E1) after 1 (1.06 [0.85–1.33]) and 5 days (1.08 [0.86–1.35]); and artemether had no effect on the 1-OH-midazolam/midazolam ratio in plasma (marker reaction for CYP3A) after 1 (1.22 [0.90–1.65]) day but increased the ratio after 5 (1.54 [1.14–2.09]) days when given in combination compared to the drug cocktail given alone. These findings suggest differential effects of artemether on the induction or inhibition of the tested CYP450 pathways. However, metabolic ratios

Table 5.1 Effects of antimalarial drugs on pharmacokinetics of co-administered drugs

Antimalarial	Population	Design	n	Effect drug dosing	Antimalarial dosing	Effects of antimalarials on PK of drugs								Reference
						Analyte	AUC	Cmax	Cmin	Tmax	Vd/F	CL/F	t1/2	
Amodiaquine	Healthy (Swedish Caucasian, 9 M) Age: 33 years (mean)	Open label Prospective Cross over	12	600 mg × 1 orally	Caffeine (100 mg) Debrisoquine (10 mg) Omeprazole (20 mg) Losartan (25 mg)	Caffeine Debrisoquine Omeprazole Losartan (cocktail)	ND (see text)	ND	ND	ND	ND	ND	ND	Wennerholm et al. (2006)
Artemether	Healthy volunteers	Open label Prospective Cross over	15	Cocktail of caffeine (100 mg), coumarin (5 mg), midazolam (7.5 mg), mephenytoin (100 mg), metoprolol (100 mg), and chlorzoxazone (250 mg) on days 1 and 5	100 mg orally once daily for 5 days	Caffeine/coumarin/midazolam/mephenytoin/metoprolol/chlorzoxazone	ND (see text)	ND	ND	ND	ND	ND	ND	Asimus et al. (2007)
Artemisinin	Healthy male Vietnamese subjects	Open label Prospective Cross over	9	20 mg omeprazole orally × 1	500 mg orally daily × 7 days	R-omeprazole (after 1 dose of artemisinin)	ND (did not compared to omeprazole only control—see text)	ND	ND	ND	ND	ND	ND	Mihara et al. (1999)
Artemisinin	Healthy male Vietnamese subjects	Open label Prospective Cross over	9 (8 extensive metabolizers)	20 mg omeprazole orally × 1	500 mg orally daily × 7 days	R-omeprazole (after 7 doses of artemisinin)	ND (did not compared to omeprazole only control—see text)	ND	ND	ND	ND	ND	ND	Mihara et al. (1999)
Artemisinin	Healthy male Vietnamese subjects	Open label Prospective Cross over	9 (8 extensive metabolizers)	20 mg omeprazole orally × 1	500 mg orally daily × 7 days	R-omeprazole (after 14 doses of artemisinin)	ND (did not compared to omeprazole only control—see text)	ND	ND	ND	ND	ND	ND	Mihara et al. (1999)

(continued)

Table 5.1 (continued)

Antimalarial	Population	Design	n	Effect drug dosing	Antimalarial dosing	Effects of antimalarials on PK of drugs								Reference
						Analyte	AUC	Cmax	Cmin	Tmax	Vd/F	CL/F	t1/2	
Artemisinin	Healthy male Vietnamese subjects	Open label Prospective Cross over	9 (8 extensive metabolizers)	20 mg omeprazole orally × 1	500 mg orally daily × 7 days	S-omeprazole (after 1 dose of artemisinin)	ND (did not compared to omeprazole only control—see text)	ND	ND	ND	ND	ND	ND	Mihara et al. (1999)
Artemisinin	Healthy male Vietnamese subjects	Open label Prospective Cross over	9 (8 extensive metabolizers)	20 mg omeprazole orally × 1	500 mg orally daily × 7 days	S-omeprazole (after 7 doses of artemisinin)	ND (did not compared to omeprazole only control—see text)	ND	ND	ND	ND	ND	ND	Mihara et al. (1999)
Artemisinin	Healthy male Vietnamese subjects	Open label Prospective Cross over	9 (8 extensive metabolizers)	20 mg omeprazole orally × 1	500 mg orally daily × 7 days	S-omeprazole (after 14 doses of artemisinin)	ND (did not compared to omeprazole only control—see text)	ND	ND	ND	ND	ND	ND	Mihara et al. (1999)
Artemisinin	Healthy male Vietnamese subjects	Open label Prospective Cross over	9 (8 extensive metabolizers)	20 mg omeprazole orally × 1	500 mg orally daily × 7 days	R-5 hydroxyomeprazole (after 1 dose of artemisinin)	ND (did not compared to omeprazole only control—see text)	ND	ND	ND	ND	ND	ND	Mihara et al. (1999)
Artemisinin	Healthy male Vietnamese subjects	Open label Prospective Cross over	9 (8 extensive metabolizers)	20 mg omeprazole orally × 1	500 mg orally daily × 7 days	R-5 hydroxyomeprazole (after 1 dose of artemisinin)	ND (did not compared to omeprazole only control—see text)	ND	ND	ND	ND	ND	ND	Mihara et al. (1999)
Artemisinin	Healthy male Vietnamese subjects	Open label Prospective Cross over	9 (8 extensive metabolizers)	20 mg omeprazole orally × 1	500 mg orally daily × 7 days	R-5 hydroxyomeprazole (after 1 dose of artemisinin)	ND (did not compared to omeprazole only control—see text)	ND	ND	ND	ND	ND	ND	Mihara et al. (1999)

Artemisinin	Healthy male Vietnamese subjects	Open label Prospective Cross over	9 (8 extensive metabolizers)	20 mg omeprazole orally × 1	500 mg orally daily × 7 days	S-5 hydroxyomeprazole (after 1 dose of artemisinin)	ND (did not compared to omeprazole only control—see text)	ND	ND	ND	ND	ND	ND	Mihara et al. (1999)
Artemisinin	Healthy male Vietnamese subjects	Open label Prospective Cross over	9 (8 extensive metabolizers)	20 mg omeprazole orally × 1	500 mg orally daily × 7 days	S-5 hydroxyomeprazole (after 1 dose of artemisinin)	ND (did not compared to omeprazole only control—see text)	ND	ND	ND	ND	ND	ND	Mihara et al. (1999)
Artemisinin	Healthy male Vietnamese subjects	Open label Prospective Cross over	9 (8 extensive metabolizers)	20 mg omeprazole orally × 1	500 mg orally daily × 7 days	S-5 hydroxyomeprazole (after 1 dose of artemisinin)	ND (did not compared to omeprazole only control—see text)	ND	ND	ND	ND	ND	ND	Mihara et al. (1999)
Artemisinin	Healthy volunteers (6 M) Age: 36–54 years old	Open label Prospective Cross over	10	136.5 mg orally × 1	500 mg orally × 1	Caffeine	↔	↔	ND	↔	ND	↔	↔	Bapiro et al. (2005)
Artemisinin	Healthy volunteers	Open label Prospective Cross over	15	Cocktail of caffeine (100 mg), coumarin (5 mg), midazolam (7.5 mg), mephenytoin (100 mg), metoprolol (100 mg), and chlorzoxazone (250 mg) on days 1 and 5	500 mg orally once daily for 5 days	Caffeine/coumarin/midazolam/mephenytoin/metoprolol/chlorzoxazone	ND (see text)	ND	ND	ND	ND	ND	ND	Asimus et al. (2007)

(continued)

Table 5.1 (continued)

Antimalarial	Population	Design	n	Effect drug dosing	Antimalarial dosing	Effects of antimalarials on PK of drugs								Reference
						Analyte	AUC	Cmax	Cmin	Tmax	Vd/F	CL/F	t1/2	
Dihydroartemisinin	Healthy volunteers	Open label Prospective Cross over	14	Cocktail of caffeine (100 mg), coumarin (5 mg), midazolam (7.5 mg), mephenytoin (100 mg), metoprolol (100 mg), and chlorzoxazone (250 mg) on days 1 and 5	60 mg orally once daily for 5 days	Caffeine/coumarin/midazolam/mephenytoin/metoprolol/chlorzoxazone	ND (see text)	ND	ND	ND	ND	ND	ND	Asimus et al. (2007)
Artemisinin	Healthy male Vietnamese subjects Age: 32 years (avg) Wt: 58 kg	Open label Prospective Randomized Cross over	12	200 mg orally × 1	500 mg orally daily for 5 days	Coumarin (hydroxycoumarin)	↔	ND	ND	ND	ND	ND	ND	Asimus et al. (2007)
Artemisinin	Healthy male Vietnamese subjects Age: 32 years (avg) Wt: 58 kg	Open label Prospective Randomized Cross over	12	200 mg orally × 1	500 mg orally daily for 5 days	Coumarin (hydroxycoumarin glucuronide)	↑(26 %)	ND	ND	ND	ND	ND	ND	Asimus et al. (2008)
Artemisinin	Healthy male Vietnamese subjects Age: 32 years (avg) Wt: 58 kg	Open label Prospective Randomized Cross over	12	4 mg piece of gum orally × 1	500 mg orally daily for 5 days	Nicotine	↓(46 %)	ND	ND	ND	ND	ND	ND	Asimus et al. (2008)
Artemisinin	Healthy male Vietnamese subjects Age: 32 years (avg) Wt: 58 kg	Open label Prospective Randomized Cross over	12	4 mg piece of gum orally × 1	500 mg orally daily for 5 days	Nicotine (Cotinine)	↓(8 %)	ND	ND	ND	ND	ND	ND	Asimus et al. (2008)

Artesunate	Healthy volunteers	Open label Prospective Cross over	15	Cocktail of caffeine (100 mg), coumarin (5 mg), midazolam (7.5 mg), mephenytoin (100 mg), metoprolol (100 mg), and chlorzoxazone (250 mg) on days 1 and 5	100 mg orally once daily for 5 days	Caffeine/coumarin/midazolam/mephenytoin/metoprolol/chlorzoxazone	ND (see text)	ND	ND	ND	ND	ND	ND	Asimus et al. (2007)
Atovaquone	Healthy (all M) Age: 24 years (median) Wt: 70 kg (median)	Open label Prospective Randomized Cross over	12	1,000 mg × 2 orally	600 mg × 1 orally	Phenytoin	↔	↔	ND	↔	↔	↔	↔	Davis et al. (1996)
Atovaquone	HIV-infected (5 M) Age: 31 years (median)	Open label Prospective Cross over	6	160/800 mg orally every 12 ours × 1 week	500 mg orally daily (with food) × 2 weeks	Trimethoprim-sulfamethoxazole	ND (see text)	ND	ND	ND	ND	ND	ND	Falloon et al. (1999)
Chloroquine	Healthy (all M) Age: 23.4 ± 3.7 years Wt: 72.7 ± 7.2 kg None poor metabolizers	Open label Prospective Cross over	14	Cocktail of caffeine (100 mg), mephenytoin (100 mg), debrisoquine (10 mg), chlorzoxazone (250 mg), and dapsone (100 mg)	250 mg orally daily × 1 and 7 days	Caffeine	ND (see text)	ND	ND	ND	ND	ND	ND	Adedoyin et al. (1998a
Chloroquine	Healthy (all M) Age: 23.4 ± 3.7 years Wt: 72.7 ± 7.2 kg None poor metabolizers	Open label Prospective Cross over	14	Cocktail of caffeine (100 mg), mephenytoin (100 mg), debrisoquine (10 mg), chlorzoxazone (250 mg), and dapsone (100 mg)	250 mg orally daily × 1 and 7 days	Mephenytoin	ND (see text)	ND	ND	ND	ND	ND	ND	Adedoyin et al. (1998a)

(continued)

Table 5.1 (continued)

Antimalarial	Population	Design	n	Effect drug dosing	Antimalarial dosing	Effects of antimalarials on PK of drugs								Reference
						Analyte	AUC	Cmax	Cmin	Tmax	Vd/F	CL/F	t1/2	
Chloroquine	Healthy (all M) Age: 23.4 ± 3.7 years Wt: 72.7 ± 7.2 kg None poor metabolizers	Open label Prospective Cross over	14	Cocktail of caffeine (100 mg), mephenytoin (100 mg), debrisoquine (10 mg), chlorzoxazone (250 mg), and dapsone (100 mg)	250 mg orally daily × 1 and 7 days	debrisoquine	ND (see text)	ND	ND	ND	ND	ND	ND	Adedoyin et al. (1998a)
Chloroquine	Healthy (all M) Age: 23.4 ± 3.7 years Wt: 72.7 ± 7.2 kg None poor metabolizers	Open label Prospective Cross over	14	Cocktail of caffeine (100 mg), mephenytoin (100 mg), debrisoquine (10 mg), chlorzoxazone (250 mg), and dapsone (100 mg)	250 mg orally daily × 1 and 7 days	chlorzoxazone	ND (see text)	ND	ND	ND	ND	ND	ND	Adedoyin et al. (1998a)
Chloroquine	Heatlhy (Zambians, all M) Age: 21–29 years	Open label Prospective Cross over	10	10 mg orally × 1	1,500 mg orally × 1	Debrisoquine	ND (see text)	ND	ND	ND	ND	ND	ND	Simooya et al. (1998)
Chloroquine	Healthy (Zambians, all M) Age: 27 ± 4 years Wt. 60.8 ± 5.6 kg	Open label Prospective Cross over	11	Not specified	500 mg orally × 1 (prophylaxis dose)	Debrisoquine	ND (see text)	ND	ND	ND	ND	ND	ND	Masimirembwa et al. (1996)
Chloroquine	Healthy (Swedish) Age: 38 ± 8 years Wt: 70.2 ± 13 kg	Open label Prospective Cross over	12	Not specified	500 mg orally Q8H × 3	Debrisoquine	ND (see text)	ND	ND	ND	ND	ND	ND	Masimirembwa et al. (1996)

Chloroquine	Healthy (Zambians, all M) Age: 27 ± 4 years Wt. 60.8 ± 5.6 kg	Open label Prospective Cross over	11	Not specified	500 mg orally × 1 (prophylaxis dose)	S-Mephentyoin	ND (see text)	ND	ND	ND	ND	ND	ND	Masimirembwa et al. (1996)
Chloroquine	Healthy (Swedish) Age: 38 ± 8 years Wt: 70.2 ± 13 kg	Open label Prospective Cross over	12	Not specified	500 mg orally Q8H × 3	S-Mephentyoin	ND (see text)	ND	ND	ND	ND	ND	ND	Masimirembwa et al. (1996)
Chloroquine	Healthy (all M) Age: 23 years (mean) Wt: 58 kg (mean)	Open label Prospective Cross over	7	1,000 mg orally × 1	1,000 mg orally × 1	Ampicillin	ND (see text)	ND	ND	ND	ND	ND	ND	Ali (1985)
Chloroquine	Schizophrenic patients Age: 18–40 years old	Open label Prospective Cross over	5	Steady-state dosing (400 mg or 500 mg orally daily)	400 mg orally × 1	Chlorpromazine	ND (see text)	ND	ND	ND	ND	ND	ND	Makanjuola et al. (1988)
Chloroquine	Healthy volunteers Age: 23–28 years old Wt: 55–65 kg	Open label Prospective Randomized Cross over	6	50 mg orally × 1	300 mg orally × 1	Imipramine	ND	↔	ND	↔	↔	↔	↔	Onyeji et al. (1993)
Chloroquine	Healthy volunteers (all M) Age: 19–31 years old	Open label Prospective Cross over	5	500 mg orally × 1	600 mg orally × 1	Ciprofloxacin	↓(43 %)	↓(18 %)	ND	↔	ND	ND	ND	Ilo et al. (2006)
Chloroquine	Healthy volunteers (19 M) Age: 19.3 years (mean) Wt: 89.5 kg (mean)	Open label Prospective Cross over	24	1 g orally daily × 3 days	1 g orally × 2 days, then 500 mg orally × 1 day	Azithromycin	↔	↔	ND	ND	ND	ND	↔	Cook et al. (2006)
Chloroquine	Healthy volunteers	Open label Prospective Cross over	6	600 mg orally × 1	250 mg orally × 1	Antipyrine	ND (see text)	ND	ND	ND	ND	ND	ND	Back et al. (1983)

(continued)

Table 5.1 (continued)

Antimalarial	Population	Design	n	Effect drug dosing	Antimalarial dosing	Effects of antimalarials on PK of drugs								Reference
						Analyte	AUC	Cmax	Cmin	Tmax	Vd/F	CL/F	t1/2	
Mefloquine	Healthy volunteers (all M) Age: 28–36 years	Open label Prospective Cross over	6	300 mg orally × 1	750 mg orally × 1	Antipyrine	ND (see text)	ND	ND	ND	ND	ND	ND	Riviere et al. (1985)
Mefloquine	Healthy volunteers	Open label Prospective Cross over	11	200 mg orally × 1, then 200 mg orally after last mefloquine dose (single dose)	250 mg orally daily for 3 days, then once weekly for 2 weeks	Ritonavir	↔	↔	ND	↔	ND	↔	↔	Khaliq et al. (2001)
Mefloquine	Healthy volunteers	Open label Prospective Cross over	12	200 mg orally twice daily for 7 days, then same dose again for 7 days with last mefloquine dose (steady-state)	250 mg orally daily for 3 days, then once weekly for 4 weeks	Ritonavir	↓(29 %)	↑(32 %)	ND	↔	ND	↑(57 %)	↔	Khaliq et al. (2001)
Primaquine	Healthy volunteers	Open label Prospective Cross over	6	600 mg orally × 1	45 mg orally × 1	Antipyrine	ND (see text)	ND	ND	ND	ND	ND	ND	Back et al. (1983)
Proguanil	Healthy volunteers (5 M) Age:25–35 years Wt: 55–72 kg	Open label Prospective Cross over	7	500 mg orally × 1	200 mg orally × 1	Cloxacillin	ND (see text)	ND	ND	ND	ND	ND	ND	Babalola et al. (2002)
Pyrimethamine	HIV-infected patients with *Toxoplasma gondii*	Open label Prospective Cross over	10	200 mg oral loading dose, then 50 mg orally daily × 3 weeks (steady-state)	100 mg orally × 1	Zidovudine	↔	↔	ND	ND	↔	↔	↔	Jacobson et al. (1996)
Pyrimethamine	Healthy volunteers (all M) Age: 28.0 ± 4.5 years (mean ± SD) Wt: 63.9 ± 6.9 kg	Open label Prospective Cross over	8	250 mg orally × 1	50 mg orally × 1	Metformin	↑(35 %)	↔	ND	ND	ND	ND	ND	Kusuhara et al. (2011)

Quinine	Healthy volunteers + in patients (5 M) Age: 21–57 years Wt:	Open label Prospective Cross over	6	1 mg intravenous dose × 1	200 mg orally Q8h for 4 days	Digoxin	ND (see text)	ND	ND	ND	↔	↓(26 %)	ND	Wandell et al. (1980)
Quinine	Healthy volunteers (all M) Age: 23–33 years	Open label Prospective Cross over	7	1 mg loading dose (oral), then 0.1875 mg twice daily × 2 weeks (steady-state)	250 mg orally daily × 1 week (steady-state)	Digoxin	ND (see text)	ND	ND	ND	ND	ND	ND	Pedersen et al. (1985)
Quinine	Healthy volunteers (all M) Age: 23–33 years	Open label Prospective Cross over	7	1 mg loading dose (oral), then 0.1875 mg twice daily × 2 weeks (steady-state)	250 mg orally 3 times daily × 1 week (steady-state)	Digoxin	ND(see text)	ND	ND	ND	ND	ND	ND	Pedersen et al. (1985)
Quinine	Healthy volunteers (7 rapid metabolizer, 3 slow metabolizer)	Open label Prospective Cross over	10	25 mg orally × 1	750 mg orally daily for 2 days	Desipramine	ND(see text)	ND	ND	ND	ND	ND	ND	Steiner et al. (1988)
Quinine	Healthy volunteers (all M) Age: 26 years (mean) Wt: 77 kg	Open label Prospective Cross over	10	150 mg infusion × 1	500 mg quinine orally Q12h × 3 doses	Flecainide	↑(21 %)	ND	ND	ND	↔	↓(16 %)	↑(20 %)	Munafo et al. (1990)
Quinine	Healthy volunteers	Open label Prospective Cross over	6	200 mg orally × 1	600 mg orally × 1	Carbamazepine	↑(104 %)	↑(57 %)	ND	ND	ND	ND	ND	Amabeoku et al. (1993)
Quinine	Healthy volunteers	Open label Prospective Cross over	6	120 mg orally × 1	600 mg orally × 1	Phenobarbital	↑(80 %)	↑(53 %)	ND	ND	ND	ND	ND	Amabeoku et al. (1993)
Quinine	Healthy volunteers	Open label Prospective Cross over	6	200 mg orally × 1	600 mg orally × 1	Phenytoin	↔	↔	ND	ND	ND	ND	ND	Amabeoku et al. (1993)
Quinine	Healthy volunteers	Open label Prospective Cross over	10	Steady-state 200 mg orally every 12 h × 9 days	600 mg orally × 1	Ritonavir	↑(21 %)	↑(14 %)	↑(66 %)	↔	ND	ND	↑(32 %)	Soyinka et al. (2010)

(continued)

Table 5.1 (continued)

Antimalarial	Population	Design	n	Effect drug dosing	Antimalarial dosing	Effects of antimalarials on PK of drugs								Reference
						Analyte	AUC	Cmax	Cmin	Tmax	Vd/F	CL/F	t1/2	
Quinine	Healthy volunteers Age: 18–55 years	Open label Prospective Cross over	12	Steady-state 400/100 (lopinavir/ritonavir) orally twice daily for 12 days	648 mg orally × 1	Lopinavir	↔	ND	ND	ND	ND	ND	ND	Nyunt et al. (2012)
Quinine	Healthy volunteers Age: 18–55 years	Open label Prospective Cross over	12	Steady-state 400/100 (lopinavir/ritonavir) orally twice daily for 12 days	648 mg orally × 1	Ritonavir	↔	ND	ND	ND	ND	ND	ND	Nyunt et al. (2012)

AUC area under the plasma concentration-time curve, *CL/F* apparent oral clearance, *Cmax* maximal concentration, *Cmin* minimal concentration, *M* male, *ND* data not available, *t1/2* half-life, *PK* pharmacokinetics, *Tmax* time to reach maximum concentration, *Vd/F* apparent volume of distribution, *Wt* weight, ↔ = no significant change

were not supported by specific pharmacokinetic measurements and the findings also rely on the assumption that the probes were specific toward each CYP450 pathway under these experimental conditions.

5.3 Effects of Artemisinin on the Pharmacokinetics of Drugs

The effects of artemisinin (500 mg orally daily for 1 dose or 7 doses) on the disposition of omeprazole (20 mg orally as a single dose) were studied by Svensson et al. (1998) and Mihara et al. (1999) in healthy male volunteers of Vietnamese ethnicity (n = 9), using a prospective, open label, cross over design. Steady-state artemisinin significantly increased the oral clearance of both racemic forms of omeprazole (no absolute values reported), elevated the AUC ratio between R-5-hydroxyomeprazole to R-omeprazole (4.9 [2.5–9.6] vs. 3.0 [1.6–6.0, mean [95 % CI], but had little effect on the AUC ratio between omeprazole sulfphone and s-omeprazole, the latter indicating a stereoselective effect. Unfortunately, no other statistical comparisons were made between the combination treatment and omeprazole alone in the study. These findings were attributed by the authors to the inductive effects of artemisinin toward CYP2C19, the principal enzyme responsible for the 5-hydroxylation of omeprazole (Karam et al. 1996); however, such correlations may be difficult to establish since other CYP450 enzymes are also known to metabolize omeprazole (Yamazaki et al. 1997).

The effects of artemisinin (single oral dose of 500 mg) on the disposition of caffeine (single oral dose of 136.5 mg) were examined by Bapiro et al. (2005) in healthy volunteers (n = 10), using a prospective, open label, cross over design. Single-dose artemisinin did not affect the Cmax (16.58 ± 5.68 vs. 14.43 ± 3.82 μmol/L, mean ± SD), Tmax (2.21 ± 1.29 vs. 1.38 ± 0.58 h), t1/2 (12.49 ± 2.00 vs. 11.91 ± 4.51 h), AUC_{last} (231.43 ± 70.61 vs. 176.58 ± 54.43 μmol h/L) and CL/F (0.033 ± 0.012 vs. 0.051 ± 0.027 L/h/kg), but significantly reduced the paraxanthine (metabolite) to caffeine ratio measured 4 h post dose (0.077 ± 0.023 vs. 0.225 ± 0.050) of caffeine when given in combination compared to caffeine alone, respectively. The mechanism of the observed reduction in the paraxanthine to caffeine ratio is supported by the known metabolic properties of these agents: that caffeine is primarily metabolized by CYP1A2 in the formation of paraxanthine (Gu et al. 1992) and artemisnin has been shown to extensively inhibit CYP1A2 activity in vitro (Bapiro et al. 2001). Moreover, the lack of significant changes in caffeine pharmacokinetics in the presence of artemisnin may be explained by the activation/utilization of alternative caffeine metabolic pathways since caffeine is also a known substrate for other CYP450 isoenzymes (Ha et al. 1996) or the fact that artemisnin is a relatively non-potent inhibitor of CYP1A2, as demonstrated by a high Ki value determined in vitro (Bapiro et al. 2001). These findings suggest that artemisinin may inhibit the metabolism of CYP1A2-catalyzed substrates, but depending on the metabolic

properties of the affected drug (i.e. the presence of alternative, minor metabolic pathways), the interaction may not be clinically significant, as would be in the case of caffeine.

Asimus et al. (2007) studied the effects (1 and 5 doses) of artemisinin (500 mg orally daily) on the metabolic ratios of single oral doses of a CYP450 probe substrate cocktail consisting of caffeine (100 mg), coumarin (5 mg), midazolam (7.5 mg), mephenytoin (100 mg), metoprolol (100 mg), and chlorzoxazone (250 mg) in healthy volunteers (n = 14–15) using a prospective, open label, cross over design. Artemisinin significantly decreased the paraxanthine/caffeine ratio (marker reaction for CYP1A2) in plasma after 1 (0.27 [0.18–0.39], mean [98.75 % CI]) and 5 (0.59 [0.41–0.85]) doses; artemisinin had little effect on the ratio of 7-OH-coumarin excreted in the urine (marker reaction for CYP2A6) after 1 (0.74 [0.40–1.40]) or 5 days (0.87 [0.48–1.60]); artemisinin had no effect on the 4-OH-mephenytoin/mephenytoin ratio in plasma (marker reaction for CYP2C19) after 1 (0.95 [0.83–1.09] day but increased the ratio after 5 (1.69 [1.47–1.94]) days; artemisinin decreased the OH-metoprolol/metoprolol ratio in plasma (marker reaction for CYP2D6) after 1 (0.82 [0.70–0.96] day but had no effects after 5 days (1.10 [0.94–1.29]); artemisinin decreased the 6-OH-chlorzoxzone/chlorzoxazone ratio in plasma (marker reaction for CYP2E1) after 1 (0.68 [0.54–0.86]) and 5 days (0.74 [0.58–0.94]); and artemisinin increased the 1-OH-midazolam/midazolam ratio in plasma (marker reaction for CYP3A) after 1 (1.60 [1.26–2.02]) and 5 (2.66 [2.10–3.36]) days when given in combination compared to the drug cocktail given alone. These findings suggest differential effects of artemisinin on the induction or inhibition of the tested CYP450 pathways. However, metabolic ratios were not supported by specific pharmacokinetic measurements and the findings also rely on the assumption that the probes were specific toward each CYP450 pathway under these experimental conditions.

Asimus et al. (2007) studied the effects (1 and 5 doses) dihydroartemisinin (60 mg orally daily) on the metabolic ratios of single oral doses of a CYP450 probe substrate cocktail consisting of caffeine (100 mg), coumarin (5 mg), midazolam (7.5 mg), mephenytoin (100 mg), metoprolol (100 mg), and chlorzoxazone (250 mg) in healthy volunteers (n = 14–15), using a prospective, open label, cross over design. Dihydroartemisinin significantly decreased the paraxanthine/caffeine ratio (marker reaction for CYP1A2) in plasma after 1 (0.27 [0.18–0.39], mean [98.75 % CI]) and 5 (0.59 [0.41–0.85]) doses; dihydroartemisinin had little effect on the ratio of 7-OH-coumarin excreted in the urine (marker reaction for CYP2A6) after 1 (0.74 [0.40–1.40]) or 5 (0.87 [0.48–1.60]) days; dihydroartemisinin had no effects on the 4-OH-mephenytoin/mephenytoin ratio in plasma (marker reaction for CYP2C19) after 1 (0.95 [0.83–1.09] day but increased the ratio after 5 (1.69 [1.47–1.94]) days; dihydroartemisinin decreased the OH-metoprolol/metoprolol ratio in plasma (marker reaction for CYP2D6) after 1 (0.82 [0.70–0.96] day but had no effect after 5 days (1.10 [0.94–1.29]); dihydroartemisinin decreased the 6-OH-chlorzoxzone/chlorzoxazone ratio in plasma (marker reaction for CYP2E1) after 1 (0.68 [0.54–0.86]) and 5 (0.74 [0.58–0.94]) days; and dihydroartemisinin increased the 1-OH-midazolam/midazolam ratio in plasma

(marker reaction for CYP3A) after 1 (1.60 [1.26–2.02]) and 5 (2.66 [2.10–3.36]) days when given in combination compared to the drug cocktail given alone. These findings suggest differential effects of dihydroartemisinin on the induction or inhibition of the tested CYP450 pathways. However, metabolic ratios were not supported by specific pharmacokinetic measurements and the findings also rely on the assumption that the probes were specific toward each CYP450 pathway under these experimental conditions.

Asimus et al. (2008) studied the effects of artemisinin (as a single 500 mg oral dose) on the dispositions of coumarin (200 mg orally × 1) and nicotine (4 mg gum chewed × 1), both probe substrates for CYP2A6, in healthy male volunteers of Vietnamese ethnicity (n = 12) using a prospective, open label, randomized cross over design. Artemisinin did not change the total amount of 7-OH coumarin (sum of free and glucuronidated drug), the main metabolite of coumarin, excreted in the urine (842 ± 174 vs. 755 ± 224 μmol, mean ± SD) or the AUC_{last} (0.206 [0.152–0.279] vs. 0.281 [0.204–0.389] μmol h/L, mean [95 % CI]) of 7-OH coumarin in plasma, when given in combination compared to coumarin alone, respectively. On the other hand, artemisinin significantly increased the AUC_{last} of the 7-OH coumarin glucuronide (68.7 [58.9–80.1] vs. 54.7 [41.9–71.4] μmol h/L) which resulted in an increased ratio between the glucuronide to 7-OH coumarin. In contrast, artemisinin significantly decreased the nicotine AUC_{last} in plasma (0.293 [0.131–0.653] vs. 0.547 [0.292–1.02] μmol h/L), decreased cotinine, the major metabolite of nicotine, AUC_{last} in plasma (9.72 [6.74–14.0] vs. 10.6 [5.91–19.2] μmol h/L), but had no effects on the cotinine to nicotine ratio, when given in combination compared to nicotine alone, respectively. No other pharmacokinetic parameters were reported by the authors. Both coumarin and nicotine are metabolized primarily by CYP2A6 (Cashman et al. 1992; Pelkonen et al. 2000) and these mixed results do not provide conclusive evidence that artemisinin may have inductive effects toward this isoenzyme. For example, a lack of change in hydroxycoumarin exposure and a reduction in cotinine exposure are contradictory to this claim. Unfortunately, other pharmacokinetic parameters (e.g. coumarin exposure), which may have provided additional support to the induction hypothesis, were also lacking in the study.

5.4 Effects of Artesunate on the Pharmacokinetics of Drugs

Asimus et al. (2007) studied the effects (1 and 5 doses) of artesunate (100 mg orally) on the metabolic ratios of single oral doses of a CYP450 probe substrate cocktail consisting of caffeine (100 mg), coumarin (5 mg), midazolam (7.5 mg), mephenytoin (100 mg), metoprolol (100 mg), and chlorzoxazone (250 mg) in healthy volunteers (n = 14–15), using a prospective, open label, cross over design. Artesunate had little effect on the paraxanthine/caffeine ratio (marker reaction for CYP1A2) in plasma after 1 (0.87 [0.69–1.09], mean [98.75 % CI]) and 5 (1.00 [0.80–1.26]) doses; artesunate had little effect on the ratio of 7-OH-coumarin

excreted in the urine (marker reaction for CYP2A6) after 1 (0.73 [0.38–1.44]) or 5 (0.60 [0.30–1.17]) days; artesunate had no effect on the 4-OH-mephenytoin/mephenytoin ratio in plasma (marker reaction for CYP2C19) after 1 (0.91 [0.73–1.14] and 5 (1.12 [0.89–1.40]) days; artesunate had little effect on the OH-metoprolol/metoprolol ratio in plasma (marker reaction for CYP2D6) after 1 (0.90 [0.79–1.04] and 5 (1.02 [0.89–1.18]) days; artesunate had no effects on the 6-OH-chlorzoxzone/chlorzoxazone ratio in plasma (marker reaction for CYP2E1) after 1 (0.96 [0.73–1.26]) and 5 (1.09 [0.83–1.43]) days; artesunate and had little effect toward the 1-OH-midazolam/midazolam ratio in plasma (marker reaction for CYP3A) after 1 (1.17 [0.94–1.47]) and 5 (1.25 [1.00–1.56]) days when given in combination compared to the drug cocktail given alone. These findings suggest differential effects of artesunate on the induction or inhibition of the tested CYP450 pathways. However, metabolic ratios were not supported by specific pharmacokinetic measurements and the findings also rely on the assumption that the probes were specific toward each CYP450 pathway under these experimental conditions.

5.5 Effects of Atovaquone on the Pharmacokinetics of Drugs

Davis et al. (1996) studied the effects of a single oral dose of atovaquone (2,000 mg) on the pharmacokinetics of a single oral dose of phenytoin (300 mg) in healthy volunteers using a prospective, open label, randomized cross over design in 12 healthy, young male subjects. Little effect of atovaquone on the pharmacokinetics of phenytoin was observed, as evident by similar Cmax (10.57 ± 1.84 vs. 10.93 ± 1.97 mg/L, mean $\pm$ SEM), Tmax (3–10 vs. 3–10 h, range), unbound AUC (21.7 ± 11 vs. 22.4 ± 12.1 mg h/L), total AUC (456 ± 163 vs. 464 ± 152 mg h/L), CL/F (24.7 ± 7.7 vs. 23.8 ± 8.2 mL/min), and V/F (48 ± 9 vs. 46 ± 9 L) in subjects receiving phenytoin alone compared to the combination, respectively. Likewise, atovaquone had little effect on the amount of conjugated and unconjugated excreted phenytoin metabolite (HPPH, not defined in the paper). These findings are supported by the in vitro data that atovaquone does not inhibit, or at most is a weak inhibitor of, CYP450 enzymes responsible for the oxidation of phenytoin (Bapiro et al. 2001). The effects of atovaquone on conjugation enzymes remain to be elucidated, although these data suggest little effect on phenytoin glucuronidation. Likewise, these findings also support the lack of protein binding displacement by atovaquone, which is strongly protein bound in plasma, on phenytoin from its binding sites. However, these negative findings should be interpreted in the context of the small sample size and relatively large variability in the pharmacokinetic parameters obtained.

In a sub-study enrolling six volunteers with HIV infection, Falloon et al. (1999) examined the effects of steady-state atovaquone (500 mg orally) on the

pharmacokinetics of steady-state trimethoprim-sulfamethoxazole (160/800 mg orally every 12 h) in an open label, prospective, cross over design. The major finding was that atovaquone did not affect the average concentration of trimethoprim or sulfamethoxazole (with a trend toward a decrease only), although additional pharmacokinetic parameters such as Cmax, AUC, Cmin, Tmax, and t1/2 were not reported. In vitro, atovaquone has little inhibitory effect on various CYP450 isoenzymes, including CYP2C9 that is responsible for the oxidation of sulfamethoxazole, thereby supporting the in vivo findings from this study (Bapiro et al. 2001; Miller and Trepanier 2002).

5.6 Effects of Chloroquine on the Pharmacokinetics of Drugs

Adedoyin et al. (1998a) studied the effects of a single dose (250 mg) or steady-state (after 7 days of dosing) chloroquine on the urinary recovery ratios (metabolite to parent ratio) of a cocktail of 5 CYP450 selective probe substrates: caffeine (CYP1A2), mephenytoin (CYP2C19), debrisoquine (CYP2D6), chlorzoxazone (CYP2E1), and dapsone (CYP3A4) given as a single dose in 14 healthy male (none were poor metabolizers) volunteers, using a prospective, open label, linear sequence cross over design. No significant effect of chloroquine on the recovery ratios of caffeine, mephenytoin, chlorzoxazone, or dapsone was reported indicating a lack of effect on the CYP450 isoenzymes mediating the respective enzymatic reactions. However, chloroquine did have a modest but significant effect on the recovery ratio of debrisoquine after a single dose (~7 % reduction) and multiple doses (~18 % reduction), suggesting an inhibitory effect on CYP2D6. Other pharmacokinetic parameters were not reported in this study. The lack of inhibitory effects by chloroquine toward CYP1A2, CYP2C19, and CYP3A4 marker substrates in this human studies is consistent with the in vitro findings reported by Bapiro et al. (2001), whereas chloroquine's modest inhibitory effects toward the metabolism of debrisoquine, a marker reaction of CYP2D6, was supported by the in vitro findings from Bapiro et al. (2001) and Masimirembwa et al. (1995). Given that chloroquine is partially metabolized by CYP2D6 (Projean et al. 2003), it was not surprising that the proposed mechanism of inhibition was of a competitive nature (Masimirembwa et al. 1995). However, because the effect on CYP2D6 marker reaction observed in this study was quite modest, the clinical significance of this interaction should be determined, on a case-by-case basis, in the context of the pharmacokinetics of the affected drug.

Simooya et al. (1998) also studied the effects of a single dose of chloroquine (1,500 mg orally) on the urinary ratio between debrisoquine and its metabolite 4-hydroxydebrisoquine from a single oral dose of 10 mg debrisoquine (as a means to assess the inhibitory effects of chloroquine toward CYP2D6) in 10 healthy Zambian males (all extensive metabolizers of CYP2D6), using a prospective,

open label, cross over design. Urinary ratios of debrisoquine to 4-hydroxydebrisoquine were determined at 2 h, 1 week, and 2 weeks after chloroquine coadministration. Similar to the findings by Adedoyin et al. (1998b), these authors also found a significant elevation of debrisoquine/4-hydroxydebrisoquine ratio, albeit in the urine, at 2 h (3.91 [1.92–23.9] vs. 1.39 [0.72–7.93], median and range) and 1 week (4.39 [0.75–10.5] vs. 1.39 [0.72–7.93]) post combination treatment compared to single dosing, respectively, supporting an inhibitory effect of chloroquine toward CYP2D6. No other pharmacokinetic parameter was reported in this study.

Masimirembwa et al. (1996) examined the effects of a prophylactic (500 mg orally × 1) dose or loading (500 mg orally Q8H × 3) doses of chloroquine in healthy Zambian males (n = 11) and healthy Swedish males (n = 12), respectively, on the urinary metabolic ratios of debrisoquine (marker substrate for CYP2D6) and S-mephenytoin (CYP2C19), measured 6 h after chloroquine dosing, using a prospective, open label, cross over design. It was not clear what doses of debrisoquine or S-mephenytoin were used in this study or if subjects were genotyped for CYP2D6 and CYP2C19 polymorphisms. In contrast to the findings from Adedoyin et al. (1998b) and Simooya et al. (1998), neither dosage regimens of chloroquine had a significant effect on the metabolic ratios of debrisoquine, suggesting a lack of effect on CYP2D6 metabolism in this particular study. However, trends toward increased metabolic ratio of debrisoquine, indicating reduced metabolism, were evident in the prophylactic dose group (3.38 ± 3.59 vs. 3.13 ± 3.27, mean ± SEM, combination vs. control) and loading dose group (2.05 ± 2.03 vs. 1.10 ± 1.15), and the lack of statistical significance may be attributed to the small sample size (n = 11–12) and the large variability observed. No other pharmacokinetic parameters were reported to support these observations. Similar to Adedoyin et al. (1998b), however, these authors demonstrated a lack of effect on S-mephenytoin metabolic ratio, thus providing supporting evidence that chloroquine has no inhibitory effects on CYP2C19 activity. Taken together, the three in vivo studies examining the inhibitory effects of chloroquine are in overall agreement, and can be supported by in vitro data as discussed above.

Various studies on the effects of chloroquine on drugs other than CYP450 marker substrates are also available. Ali (1985) studied the effects of chloroquine on the pharmacokinetics of ampicillin in seven healthy male volunteers given a single 1 g dose of both drugs in an open label, prospective, cross over design. The main finding was a significant reduction in the percentage of ampicillin recovered in the urine after an 8-h collection (19 ± 2.9 vs. 29 ± 4.1 %, mean ± SEM) and maximum ampicillin excretion rate attained in the urine (1.73 ± 0.27 vs. 1.25 ± 0.17 mg/min) for ampicillin alone compared to the combination regimen, respectively. There was no statistically significant change, however, in the time associated with the maximum excretion rate for ampicillin. No other pharmacokinetic parameters were determined in this study. Because ampicillin is not extensively metabolized, there is very little theoretical ground to support a pharmacokinetic interaction at the drug metabolism enzyme level. Rather than an interaction through metabolism, however, the altered urinary pharmacokinetic

characteristics have been attributed by the authors to be due to the combined effects of enhanced gastric mobility and delayed gastric emptying from chloroquine administration, which work together to decrease ampicillin absorption. These observations should be confirmed, however, with further mechanistic pharmacokinetic studies measuring plasma ampicillin concentrations to confirm an interaction at the absorption site rather than an effect on ampicillin drug excretion.

The effects of a single oral dose of chloroquine (400 mg) on plasma concentrations of chlorpromazine was determined in five schizophrenic patients receiving stable doses of the antipsychotic agent (400 or 500 mg orally daily) in an open label, prospective, cross over design by Makanjuola et al. (1988). Chloroquine significantly increased the mean (3-h post dose) concentration of chlorpromazine (70 ± 15 vs. 26 ± 9 ng/mL, mean $\pm$ SEM) and chlorpromazine-hydroxide metabolite (14 ± 2 vs. 7 ± 3 ng/mL) but did not affect chlorpromazine-sulfoxide metabolite (7 ± 5 vs. 4 ± 2 ng/mL) during combination treatment compared chlorpromazine alone, respectively. These in vivo observations may be explained by the in vitro findings in human liver microsomes that the hydroxylation of chlorpromazine is primarily catalyzed by CYP1A2 and CYP2D6 (Yoshii et al. 2000), the latter isoenzyme known to be inhibited by chloroquine (Bapiro et al. 2001).

Onyeji et al. (1993) studied the effects of single-dose chloroquine (300 mg) on the pharmacokinetics of imipramine (50 mg) in healthy volunteers using an open label, prospective, randomized cross over design. The major finding was that chloroquine did not affect the pharmacokinetics of imipramine or its metabolite, desipramine, as evident by comparable Cmax (33.4 ± 3.7 vs. 29.5 ± 3.2 ng/mL, mean $\pm$ SD), Tmax (3.0 ± 1.2 vs. 3.3 ± 1.0 h), t1/2 (13.3 ± 3.7 vs. 14.6 ± 3.9 h), Cl/F (1.88 ± 0.70 vs. 1.78 ± 0.71 L/h/kg), and Vd/F (33.51 ± 7.53 vs. 34.32 ± 3.90 L/kg), for combined treatment compared to imipramine alone, respectively. Chloroquine had little effect on the pharmacokinetics of desipramine as evident by virtually identical AUC_{last} (596 ± 105 vs. 580 ± 78.37 ng h/mL, mean $\pm$ SD) and mean residence time (17.20 ± 2.0 vs. 19.15 ± 1.6 h) values, for the combination compared to the control, respectively. Since both imipramine and desipramine are substrates of CYP2D6 (Ereshefsky et al. 1995) and chloroquine an inhibitor of CYP2D6 (Bapiro et al. 2001), there exists a potential for a drug-drug interaction based on in vitro data. The negative findings from this in vivo study, however, should be interpreted in the context of the sample size ($n = 6$).

Ilo et al. (2006) studied the effects of a single oral dose of chloroquine (600 mg) on the pharmacokinetics of ciprofloxacin given as a single oral dose (500 mg) in healthy male volunteers ($n = 5$), using an open label, prospective, cross over design. Chloroquine significantly reduced the Cmax (2.8 ± 0.18 vs. 3.42 ± 2.23 μg/mL, mean $\pm$ SEM) and AUC_{∞} (6.88 ± 0.34 vs. 12.15 ± 0.68 μg h/mL) of ciprofloxacin when given in combination compared to ciprofloxacin alone, respectively. The mechanism of the interaction may be attributed to pharmacokinetic processes other than drug metabolism as chloroquine is only a weak inhibitor of CYP2D6 which does not play a role in the oxidation of ciprofloxacin. It is unknown whether the observation can be reproduced in clinical practice (i.e. steady-state dosing conditions of both agents).

Cook et al. (2006) studied the effects of chloroquine (given as 2.5 g orally divided over 3 days) on the pharmacokinetics of azithromycin (given as 3 g orally divided over 3 days) in healthy volunteers, using an open label, prospective, cross over design (n = 24). Chloroquine did not affect the Cmax (0.922 vs. 0.805 μg/mL, mean), Tmax (2.00 vs. 2.38 h), AUC_{∞} (20.5 vs. 19.9 μg h/mL) and t1/2 (73.3 vs. 74.0 h) of azithromycin, when given in combination compared to azithromycin alone, respectively, indicating a lack of pharmacokinetic interaction. No other pharmacokinetic parameters were reported in this study. These observations are supported by in vitro data that chloroquine does not have an inhibitory effect on the CYP3A4 isoenzyme known to catalyze azithromycin (Bapiro et al. 2001) in humans.

The effects of chloroquine (250 mg orally × 1) on the pharmacokinetics of antipyrine (600 mg orally × 1) was studied in 6 healthy volunteers by Back et al. (1983), using an open label, prospective, cross over design. Chloroquine did not affect the t1/2 (11.7 ± 3.5 vs. 12.5 ± 3.6 h, mean ± SD), Cl/F (2.34 ± 0.56 vs. 2.42 ± 0.99 L/h), or Vd/F (37.9 ± 9.1 vs. 39.8 ± 6.9 L) of antipyrine when measured in saliva when compared to the antipyrine alone, respectively. Little effect on the urinary clearance of antipyrine metabolites was reported (numerical data not available). No other pharmacokinetic parameters (including in plasma) were reported. These results are supported by the lack of data on metabolic drug interactions at the enzymatic level. Specifically, it has been demonstrated that the formation of 4-hydroxyantipyrine, 3-hydroxymethylantipyrine, and norantipyrine is catalyzed by human CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C18 and CYP3A4 (Engel et al. 1996), some of which are known to be minimally inhibited by chloroquine in vitro (Bapiro et al. 2001).

Obua et al. (2006) examined the pharmacokinetic interaction between chloroquine (as a single 600 mg oral dose) and sulfadoxine/pyrimethamine (as a single 1,500/75 mg oral dose) in healthy volunteers via an open label, prospective, randomized, parallel group design (n = 8). Chloroquine did not change the pharmacokinetic of pyrimethamine in plasma as evident by comparable Cmax (3.3 [2.4–4.3] vs. 3.6 [2.6–4.8] mol/L, median [range]), AUC_{last} (63 [43–82] vs. 66 [54–80] mmol h/L), and Tmax (4 [1–10] vs. 2 [2–4] h) for the combination compared to pyrimethamine alone, respectively. No other pharmacokinetic parameters were reported. Likewise, chloroquine did not affect the Cmax (463 [332–546] vs. 532 [455–649] mmol/L, median [range]), AUC_{last} (118 [99–140] vs. 122 [102–159] mmol h/L), Tmax (10 [6–24] vs. 6 [1–6] h), t1/2 (221 [154–347] vs. 229 [136–272] h), Vd/F (0.16 [0.11–0.33] vs. 0.15 [0.12–0.18] L/kg), and Cl/F (0.54 [0.45–0.58] vs. 0.39 [0.30–0.56] mL/h/kg), and bioavailability (0.97 [0.88–1.06] vs. 1) of sulfadoxine when given in combination compared to sulfadoxine alone (formulated with pyrimethamine), respectively. As discussed for the effects of pyrimethamine/sulfadoxine on the pharmacokinetics of chloroquine, this study may be limited by the small sample size and large variability. Likewise, the lack of significant pharmacokinetic interaction can be explained by the known metabolic properties of these agents that do not support an interaction at the (CYP450) enzymatic level.

5.7 Effects of Mefloquine on the Pharmacokinetics of Drugs

Riviere et al. (1985) examined the effects of single-dose (750 mg orally) mefloquine on the pharmacokinetics of a single dose of antipyrine (300 mg orally) in healthy male volunteers (n = 6), using an open label, prospective, cross over design. Mefloquine did not affect the pharmacokinetics of antipyrine in saliva, as evident by comparable t1/2 (15.2 ± 0.9 vs. 12.6 ± 3.2 h, mean ± SD), AUC (110.2 ± 23.9 vs. 100.3 ± 15.4 μg h/mL), Cl/F (2.86 ± 0.65 vs. 3.06 ± 0.46 L/h), and Vd/F (62.5 ± 128 vs. 54.2 ± 8.1 L) measured 2 h after the co-administration of mefloquine compared to antipyrine given alone, respectively. Similar pharmacokinetic profiles of antipyrine were also observed at 2 weeks post mefloquine treatment. Supporting a lack of metabolic interaction between mefloquine and antipyrine, mefloquine did not affect the formation clearance (based on amount of metabolite excreted in the urine) of 4-hydroxyantipyrine, norantipyrine, or 3-hydroxymethylantipyrine. The lack of interaction between mefloquine and antipyrine reported in this study is supported by there being no molecular or metabolic basis for the drug interaction, but the findings should be interpreted in the context of a very small sample size.

Khaliq et al. (2001) examined the effects of steady-state mefloquine (250 mg orally daily for 3 days, then once weekly for 2–4 weeks) on the disposition of steady-state ritonavir (200 mg orally twice daily for 7 days) or single-dose ritonavir (200 mg) in healthy volunteers (n = 11–12), using an open label, prospective, cross over design. Mefloquine did not change the pharmacokinetics of a single dose of ritonavir, as evident by similar AUC_{∞} (14.0 ± 6.3 vs. 13.5 ± 7.1 μgh/mL, mean ± SD), Cmax (2,225 ± 900 vs. 2,259 ± 1,190 ng/mL), t1/2 (4.4 ± 1.1 vs. 4.2 ± 1.6 h), Cl/F (292 ± 143 vs. 333 ± 230 mL/min), and Tmax (4.5 vs. 4.5 h, mean) when given in combination compared to ritonavir alone, respectively. On the other hand, mefloquine significantly decreased the AUC_{∞} (19.4 ± 9.3 vs. 27.5 ± 11.7 μg h/mL) and Cmax (3,463 ± 1,842 vs. 5,063 ± 2,468 ng/mL), increased the Cl/F (229 ± 146 vs. 146 ± 76.1 mL/min), but had little effects toward the t1/2, Tmax, or the fraction unbound of steady-state ritonavir when given in combination compared to ritonavir alone, respectively. Mefloquine had little effect on the erythromycin breath test, suggesting a lack of inhibitory effect toward CYP3A4 activities in these healthy volunteers. The discrepancies between the effects of mefloquine on single-dose compared steady-state ritonavir have been attributed by the authors to differences in study design, but these assertions need to be further investigated. Furthermore, the reduced Cmax and AUC of steady-state ritonavir in the presence of mefloquine is contradictory to the known metabolic properties of both drugs: that mefloquine is metabolized by and thus can serve as a competitive inhibitor of CYP3A4 (32) and that ritonavir is a substrate of the same isoenzyme (Hsu et al. 1998). Because the free fraction of ritonavir is unchanged, one can rule out protein binding displacement as a mechanism for the observed interaction. These negative findings, other than the potential

confounding factors of small sample size and large variability, may suggest the modulation of metabolic pathways other than CYP3A4 of ritonavir in the presence of mefloquine.

5.8 Effects of Primaquine on the Pharmacokinetics of Drugs

The effects of primaquine (45 mg orally × 1) on the pharmacokinetics of antipyrine (600 mg orally × 1) was studied in six healthy volunteers by Back et al. (1983), using an open label, prospective, cross over design. Primaquine significantly increased t1/2 (25.3 ± 3.9 vs. 12.7 ± 3.2 h, mean ± SD), decreased Cl/F (1.32 ± 0.32 vs. 3.01 ± 0.67 L/h), but had little effect on Vd/F (47.5 ± 6.3 vs. 53.3 ± 10.3 L) of antipyrine as measured in saliva when compared to the control (i.e. antipyrine administered alone), respectively. Primaquine also significantly reduced the urinary clearance of 3-hydroxymethylantipyrine (0.13 ± 0.04 vs. 0.36 ± 0.05 L/h), 4-hydroxyantipyrine (0.27 ± 0.10 vs. 0.91 ± 0.33 L/h), and norantipyrine (0.19 ± 0.07 vs. 0.43 ± 0.18 L/h) when administered in combination compared to antipyrine alone, respectively. No other pharmacokinetic parameters (including in plasma) were reported. It has been demonstrated that the formation of 4-hydroxyantipyrine, 3-hydroxymethylantipyrine, and norantipyrine are catalyzed by human CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C18 and CYP3A4 (Engel et al. 1996). Although no direct in vitro drug inhibition experiments have been conducted between the two drugs, primaquine is primarily catalyzed by CYP1A2 and CYP2D6 (Li et al. 2003) and thus can potentially serve as competitive inhibitors of antipyrine metabolism. The proposed mechanism of interaction (i.e. via CYP450 inhibition) remains to be tested in suitable in vitro models.

5.9 Effects of Proguanil on the Pharmacokinetics of Drugs

Babalola et al. (2002) examined the effects of proguanil (single oral dose of 200 mg) on the urinary excretion of cloxacillin (single oral dose of 500 mg) in healthy volunteers (n = 7), using an open label, prospective, cross over design. Proguanil significantly decreased the urinary excretion rate (7.72 ± 3.24 vs. 16.13 ± 2.92 mg/h, mean ± SD) and total amount excreted in urine (25.81 ± 8.46 vs. 49.57 ± 8.16 mg), but had little effect on the Tmax (2.43 ± 0.98 vs. 1.86 ± 1.07 h) or t1/2 (1.41 ± 0.37 vs. 0.85 ± 0.37 h) of cloxacillin in urine when given in combination compared to cloxacillin alone, respectively. Because no plasma pharmacokinetics data were reported, it was not possible to determine whether proguanil affected the hepatic intrinsic clearance, the renal excretion, and/or any other pharmacokinetic processes (e.g. absorption) of cloxacillin. No

other studies have been published on the interaction between proguanil and other types of penicillins, to our knowledge.

5.10 Effects of Pyrimethamine on the Pharmacokinetics of Drugs

Jacobson et al. (1996) evaluated the effects of steady-state pyrimethamine (200 mg oral loading dose followed by 50 mg orally daily for 3 weeks) on the pharmacokinetics of zidovudine (single oral dose of 100 mg) in HIV-infected individuals with toxoplasma gondii infection (n = 11), using a prospective, open label, cross over design. Steady-state pyrimethamine did not affect the AUC_{∞} (1224.54 ± 713.77 vs. 1265.42 ± 1360.86 μg h/mL, mean ± SD), t1/2 (1.46 ± 0.68 vs. 1.41 ± 1.08 h), Cl/F (1.76 ± 0.77 vs. 1.98 ± 0.82 L/kg/h), Vd/F (3.95 ± 3.35 vs. 3.48 ± 1.41 L/kg), or Cmax (799 ± 606 vs. 652 ± 362 ng/mL) of zidovudine when given in combination compared to zidovudine alone, respectively. Zidovudine is primarily deactivated via glucuronidation (Trapnell et al. 1998), and little is known of the effects of pyrimethamine on glucuronidation of drugs, making a metabolism-based drug interaction unlikely between this drug pair. These negative findings, however, should be interpreted in the context of the small sample and large variability.

The effects of pyrimethamine (single oral dose of 50 mg) on the pharmacokinetics of metformin (single oral dose of 250 mg) was examined by Kusuhara et al. (2011) in healthy male volunteers (n = 8), using an open label, prospective, cross over design. Pyrimethamine significantly increased the $AUC_{last/dose}$ (30.3 ± 3.1 vs. 22.4 ± 1.5 h/mL × 10^{-6}, mean ± SEM) and decreased the renal clearance (255 ± 27 vs. 395 ± 31 mL/min), but had modest yet insignificant effects on the Cmax/dose (5.38 ± 0.75 vs. 3.93 ± 0.31 $mL^{-1} \times 10^{-6}$) and fraction excreted in urine (49.8 ± 3.5 vs. 55.1 ± 2.2 %) of metformin, when given in combination compared to metformin alone, respectively. These effects are clearly attributed to the inhibitory effects of pyrimethamine toward the kidney-expressed multidrug and toxin extrusion proteins (MATE) that are responsible for the renal excretion of metformin, as demonstrated by in vitro uptake experiments using hMATE-1 and hMATE-2 expressed cells in the same study.

5.11 Effects of Quinine on the Pharmacokinetics of Drugs

Wandell et al. (1980) studied the effects of quinine (200 mg orally Q8H for 4 days) on the disposition of digoxin (single intravenous dose of 1 mg) in study subjects (n = 6), using an open label, prospective, cross over design. Quinine significantly decreased the total clearance (2.22 ± 0.07 vs. 2.98 ± 0.71 mL/min/kg, mean ± SD) and elimination rate constant (0.0141 ± 0.0033 vs. 0.0208 ± 0.0034 h^{-1}) but had

little effect on the apparent volume of distribution (9.53 ± 2.34 vs. 8.66 ± 1.98 L/kg) of digoxin in plasma when given in combination compared to digoxin alone, respectively. Quinine also increased the total amount of digoxin excreted into the urine (772.52 ± 166.30 vs. 628.29 ± 163.9 μg), decreased the digoxin nonrenal clearance (0.55 ± 0.49 vs. 1.21 ± 0.88 mL/min/kg) but had little effect on the digoxin renal clearance. No other pharmacokinetics data were provided. These findings suggest that quinine inhibited the intrinsic clearance of digoxin, possibly inhibiting enzyme(s) that catalyze the biotransformation of digoxin. However, the identities of the enzyme(s) involved remain to be elucidated.

Pedersen et al. (1985) also examined the effects of quinine (250 mg or 750 mg orally daily for 7 days) on the pharmacokinetics of digoxin (1 mg load, then 0.1875 mg twice daily orally for 2 weeks) in healthy volunteers (n = 7), in a prospective, open label, cross over study. Quinine significantly increased the plasma digoxin concentration (0.80 ± 0.18 for 250 mg dose or 0.85 ± 0.12 for 750 mg dose vs. 0.64 ± 0.12 ng/mL control, mean ± SD) in a dose-dependent manner but had little effect on the renal clearance of digoxin. An increased digoxin urinary recovery was also observed when subjects were co-administered quinine (181.5 ± 22.5 for the 250 mg dose or 203.7 ± 36.8 for the 750 mg dose vs. 181.5 ± 22.5 μg/24 h control). These results are consistent with the findings from Wandell et al. (1980) and further support the hypothesis that quinine inhibits the intrinsic clearance of digoxin.

The effects of quinine (750 mg orally daily × 2 days) on the urinary excretion of desipramine and its major metabolite, 2-hydroxydesipramine (25 mg orally × 1), were studied by Steiner et al. (1988), in an open label, prospective, cross over study in healthy volunteers (seven fast metabolizers and three slow metabolizers). Quinine had little effect on the amount of desipramine excreted in the urine in 24 h (1.02 ± .0.89 vs. 0.78 ± 0.55 μmol, mean ± SD), but significantly decreased the amount of 2-hydroxydesipramine excreted in the urine (9.19 ± 4.25 vs. 20.86 ± 5.76 μmol) when given in combination compared to desipramine alone, respectively, in fast metabolizers. On the other hand, no significant effects of quinine on the urinary excretion of desipramine and 2-hydroxydesipramine were observed in slow metabolizers. No other pharmacokinetics data (including those in plasma) were reported by the authors. The inhibitory effects of quinine on the formation of 2-hydroxyimipramine were already established in vitro as reported by von Bahr et al. (1985) in human liver microsomes. Since desipramine is a known substrate of CYP2D6 (Boni et al. 2009) and quinine is known to inhibit this enzyme (Bapiro et al. 2001), one can hypothesize that the decreased urinary excretion of the 2-hydroxydesipramine metabolite observed in this in vivo study may be due to the inhibitory effects of quinine on the CYP2D6-mediated hydroxylation of desipramine in these healthy volunteers. However, because plasma pharmacokinetic parameters were not reported in this study, there still exists the possibility that quinine may have affected other pharmacokinetic processes (e.g. absorption, renal excretion, distribution, etc) of desipramine which may have resulted in reduced urinary excretion of the metabolite. Further mechanistic experiments are needed to confirm or refute these hypotheses.

The effects of quinine (500 mg orally × 3 in 24 h) on the disposition of flecainide (single 150 mg iv infusion) were examined in healthy volunteers (n = 10), using an open label, prospective, cross over design by Munafo et al. (1990). Quinine significantly decreased Cl/F (7.6 ± 1.5 vs. 9.1 ± 1.4 mL/min/kg, mean ± SD), increased t1/2 (11.5 ± 1.5 vs. 9.6 ± 2.2 h) and AUC (237 ± 72 vs. 196 ± 56 μg min/mL), but had little effect on Vd/F (7.4 ± 1.3 vs. 7.5 ± 1.9 L/kg) or renal clearance (3.0 ± 0.7 vs. 3.0 ± 0.5 mL/min/kg) of flecainide when given in combination compared to flecainide alone, respectively. The total amount of flecainide excreted in the urine was significantly increased (49.1 ± 6.8 vs. 43.7 ± 9.0 mg) in the presence of quinine, which corresponded to decreased urinary excretion of the conjugated metabolite (m-O-dealkylated flecainide). These patterns of decreased clearance, increased AUC and t1/2, and decreased metabolite (conjugate) excretion suggest that quinine inhibited the intrinsic clearance of flecainide; these results are supported by the known metabolic properties of flecainide and quinine: that CYP2D6 is primarily responsible for the biotransformation of flecainide (Doki et al. 2009) and that quinine is a potent inhibitor of the isoenzyme (Bapiro et al. 2001).

Amabeoku et al. (1993) studied the effects of single-dose quinine (600 mg orally) on the pharmacokinetics of singles doses of carbamazepine (200 mg orally), phenobarbital (120 mg orally), or phenytoin (200 mg orally) in healthy volunteers (n = 6 per group), using an open label, prospective, cross over design. Quinine significantly increased the Cmax (5.43 ± 0.18 vs. 3.45 ± 0.32 μg/mL, mean ± SEM) and AUC_{last} (141.34 ± 5.24 vs. 69.22 ± 4.09 μg h/mL) of carbamazepine when given in combination compared to carbamazepine alone, respectively. Likewise, quinine also increased the Cmax (11.68 ± 0.78 vs. 7.61 ± 0.64 μg/mL) and AUC_{last} (368.72 ± 11.17 vs. 204.09 ± 8.71 μgh/mL) of phenobarbital when given in combination when compared to phenobarbital alone, respectively. On the other hand, quinine had no effects on the Cmax or AUC of phenytoin. These findings were associated with significantly increased urinary recovery for carbamazepine (232.48 ± 17.92 vs. 143.68 ± 20.64 μg/24 h, mean ± SEM), phenobarbital (732.64 ± 108.32 vs. 392.32 ± 48.32 μg/24 h), and phenytoin (354.88 ± 17.44 vs. 185.44 ± 35.04 μg/24 h). No other pharmacokinetic parameters were reported by the authors. Because of the enhanced urinary excretion of carbamazepine, phenobarbital, and phenytoin, the authors suggested that the interactions were unlikely attributed to the inhibitory effects of quinine toward renal excretion of drugs. Carbamazepine is primarily metabolized by CYP3A4 in the formation of the 10,11-epoxide metabolite (Kerr et al. 1994) but quinine has little or no inhibitory effect on this isoenzyme (Bapiro et al. 2001), suggesting that other metabolic pathways, which remain to be identified, may be responsible for the observed interaction. Likewise, an interaction involving CYP450 enzymes is also unlikely between quinine and phenobarbital, since the latter is primarily catalyzed by CYP2C9 or CYP2C19, neither of which are significantly inhibited by quinine (Bapiro et al. 2001). The lack of pharmacokinetic interaction observed in this study between quinine and phenytoin, however, may be supported by the fact that quinine has no inhibitory effect on the CYP450 enzymes (CYP2C19) known to

metabolize phenytoin (Bapiro et al. 2001). The contribution of other metabolic pathways or pharmacokinetic processes (i.e. drug absorption, protein binding displacement) to these observed interaction should be investigated further.

Soyinka et al. (2010) studied the pharmacokinetic interaction between ritonavir (200 mg orally every 12 h for 9 days) and quinine (600 mg single oral dose) in healthy volunteers ($n = 10$), using an open label, prospective, cross over design. Quinine modestly affected the pharmacokinetics of ritonavir, as evident by increased Cmax (11.87 ± 0.73 vs. 10.35 ± 0.78 mg/L, mean $\pm$ SD), Cmin (3.98 ± 0.44 vs. 2.40 ± 0.23 mg/L), t1/2 (4.10 ± 0.64 vs. 3.11 ± 0.27), and AUC_{last} (124.47 ± 12.44 vs. 102.88 ± 5.39 mgh/L) when given in combination compared to ritonavir alone, respectively. Evidence of the drug interaction may be supported by the known metabolic properties of ritonavir and quinine: that both drugs are primarily metabolized by CYP3A4 (Li et al. 2003; Kumar et al. 1996); thus, quinine may serve as a weak competitive inhibitor of the isoenzyme. It is not known if the modest increase in ritonavir exposure is of clinical relevance or if the effect can be reproduced in the patient population under steady-state dosing conditions for quinine.

Nyunt et al. (2012) also studied the pharmacokinetic interaction between lopinavir/ritonavir (400/100 mg orally twice daily for 12 days) and a single oral dose of quinine (648 mg) in healthy volunteers ($n = 12$), in an open label, prospective, cross over study. In contrast to findings of Soyinka et al. (2010), quinine had little effect toward the exposure of both lopinvair and ritonavir in this study. Unfortunately, other pharmacokinetic parameters for lopinavir and ritonavir were not reported which may have allowed further mechanistic interpretations. Overall, these two studies do suggest that quinine (given as a single oral dose) probably has minimal effects on the disposition of steady-state ritonavir and lopinavir.

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Chapter 6
Effects of Antimalarials on the Pharmacokinetics of Co-Administered Antimalarials

This chapter provides details of studies that describe drug interactions in which antimalarial drugs affect the pharmacokinetics of various co-administered antimalarial drugs. These antimalarials include amodiaquine, artemether, artemisinin, artesunate, atovaquone, chloroquine, dapsone, mefloquine, primaquine, proguanil, pyrimethamine, quinidine, quinine, sulfadoxine/pyrimethamine, and tafenoquine.

6.1 Effects of Amodiaquine on the Pharmacokinetics of Antimalarials

Omoruyi et al. (2007) studied the effects of amodiaquine on the pharmacokinetics of halofantrine in 10 healthy Nigerian males, using a cross over design with an 8-week washout. Subjects received a single oral dose of 500 mg halofantrine with or without pre-administered amodiaquine, given as a single 600 mg oral dose 1 day prior. The major findings were a lack of any observable or statistical change in the Tmax (6 vs. 7 h), Cmax (144 ± 53 vs. 164 ± 58 μg/L, mean ± SEM), t1/2 (142 ± 23 vs. 139 ± 28), or AUC_{∞} ($14{,}932 \pm 4{,}932$ vs. $17{,}329 \pm 5{,}988$ μg h/L) for halofantrine vs. combined therapy, respectively. Little differences were observed for desbutylhalofantrine, the major metabolite, with respect to Tmax, Cmax, mean residence time, and AUC, when subjects were given halofantrine or in combination with amodiaquine. It has been shown, in vitro, that human CYP3A4 and CYP3A5 are major isoenzymes responsible for the N-debutylation of halofantrine (Baune et al. 1999) and amodiaquine is a weak inhibitor of these enzymes (Bapiro et al. 2001; Baune et al. 1999), supporting the lack of pharmacokinetic interaction observed in this study. However, there was significant variability, which in conjunction with the relatively small and sample size, could have yielded false negative findings. As well, only single doses of halofantrine and amodiaquine were used, which may not reflect the true clinical, steady-state, situation where subjects would

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be given multiple doses of either agent. Despite the lack of pharmacokinetic interaction, however, the authors did note a prolongation of QT interval in the combination group compared to subjects on halofantrine alone, indicating a pharmacodynamic effect that appears to be unrelated to any pharmacokinetics interaction. These observations, however, need to be confirmed in the actual patient population (Table 6.1).

Orrell et al. (2008) examined the pharmacokinetic interaction between artesunate and amodiaquine in healthy volunteers of African descent. Using a randomized, prospective, and crossover design, subjects received either artesunate (4 mg/kg), amodiaquine (10 mg/kg), or the combination, as single oral doses. The study also determined the concentrations of the major metabolite for artesunate, dihydroartemisinin. The primary findings from these experiments were: significantly reduced dihydroartemisinin AUC (2044.4 ± 564.2 vs. 1410.5 ± 543.6 ng h/mL, mean $\pm$ SEM), Cmax (844.5 ± 309.4 vs. 446.2 ± 239.5 ng/mL), and increased t1/2 (1.46 ± 0.48 vs. 2.20 ± 0.85 h) and Vd/F (4.89 ± 1.67 vs. 9.68 ± 4.16 L) for subjects given artesunate alone versus in combination with amodiaquine, respectively. Although there were trends toward a decrease in Cmax, the effect was not significant. Likewise, only trends toward a decrease in the AUC and Cmax of the parent artesunate in the presence of amodiaquine were observed. These interactions are not supported by the known metabolic properties from in vitro studies. Artesunate is converted primarily by CYP2A6 to dihydroartemisinin (Li et al. 2003), which is further conjugated primarily by UGT1A9 and UGT2B7 (Ilett et al. 2002), and amodiaquine has not been shown to affect these enzyme pathways. Other explanations for the altered pharmacokinetics have not been provided by the authors and should be further investigated. One has to be cautious in applying the results of this study given the large variability and small sample size. More importantly, it is not known whether the altered pharmacokinetic characteristics of dihydroartemisinin (considered more potent than the parent artesunate) is translated to a reduced clinical effect (not determined in this study), although the combination therapy has generally been accepted by clinicians to be more effective in the treatment of *P. falciparum* than amodiaquine alone. As well, the effects of amodiaquine on artesunate pharmacokinetics and the relationship (or lack of) between pharmacokinetics-pharmacodynamics should ideally be determined in the target population under clinical (i.e. steady-state) dosing conditions.

6.2 Effects of Artemether on the Pharmacokinetics of Antimalarials

Na-Bangchang et al. (2000) studied the pharmacokinetic interactions between single oral doses of primaquine (45 mg), mefloquine (750 mg), quinine (600 mg), and artemether (300 mg) in healthy male Thai volunteers ($n = 8$), using a prospective, open label, cross over design. Artemether did not affect the pharmacokinetics

Table 6.1 Effects of co-administered antimalarial drugs on the pharmacokinetics of antimalarials

	Population	Design	N	Effect drug dosing	Affect drug dosing	Effects of antimalarials on antimalarial /metabolite PK								Reference
t						Analyte	AUC	Cmax	Cmin	Tmax	Vd/F	CL/F	t1/2	
Amodiaquine	Healthy (Nigeria, all M) Age: 22–35 years Wt. 53–72 kg	Open label Prospective Cross over	10	500 mg × 1 orally	600 mg × 1 orally 24 h before halofantrine	Halofantrine	↔	↔	ND	↔	↔	↔	↔	Omoruyi et al. (2007)
Amodiaquine	Healthy (African, 10 M) Age: 24.4 years (mean) Wt: 67.3 kg (mean)	Randomized Prospective Cross over	13	4 mg/kg × 1 orally	10 mg/kg × 1 orally	Artesunate	↔	↔	ND	↔	ND	ND	ND	Orrell et al. (2008)
Amodiaquine	Healthy (African, 10 M) Age: 24.4 years (mean) Wt: 67.3 kg (mean)	Randomized Prospective Cross over	13	4 mg/kg × 1 orally	10 mg/kg × 1 orally	Dihydroartemisinin	↓ (67 %)	↓(51 %)	ND	↔	↑(192 %)	↔	↑(157 %)	Orrell et al. (2008)
Artemether	Healthy male Thai volunteers Age: 20–29 years old Wt: 49–57 kg	Prospective Open label Cross over	8	750 mg orally × 1	300 mg orally × 1	Mefloquine	↔	↔	ND	↔	ND	ND	↔	Na-Bangchang et al. (2000)
Artemether	Healthy male Thai volunteers Age: 20–29 years old Wt: 49–57 kg	Prospective Open label Cross over	8	600 mg orally × 1	300 mg orally × 1	Quinine	↔	↔	ND	↔	ND	ND	↔	Na-Bangchang et al. (2000)
Artemether	Healthy male Thai volunteers Age: 20–29 years old Wt: 49–57 kg	Prospective Open label Cross over	8	45 mg orally × 1	300 mg orally × 1	Primaquine	↔	↔	ND	↔	ND	ND	↔	Na-Bangchang et al. (2000)

(continued)

Table 6.1 (continued)

	Population	Design	N	Effect drug dosing	Affect drug dosing	Effects of antimalarials on antimalarial /metabolite PK								Reference
t						Analyte	AUC	Cmax	Cmin	Tmax	Vd/F	CL/F	t1/2	
Artemether-lumefantrine	Healthy male volunteers Age: 19–50 years old Wt: 54.5–90.6 kg	Prospective Randomized Double blind Parallel group	14	10 mg/kg iv over 2 h × 1	80 mg/480 mg (artemether/ lumefantrine) orally × 6 doses over 60 h	Quinine	↔	↔	ND	↔	ND	ND	↔	Lefevre et al. (2002)
Artemether	Thai patients with uncomplicated falciparum malaria	Open label Prospective Parallel group	10 vs. 17 (control)	750 mg orally × 1 (24 h post artemether)	300 mg orally × 1	Mefloquine	↓(27 %)	↓(29 %)	ND	↑(133 %)	ND	ND	↔	Na-Bangchang et al. (1995)
Artemether and lumefantrine	Healthy volunteers Age: 33.7 years (mean) Wt: 73.6 kg	Open label Prospective Randomized Parallel group	14	1,000 mg orally divided in 3 doses over 12 h	80 mg artemether/ 480 mg lumefantrine orally every 12 h × 6 doses	Mefloquine	↔	↔	ND	↔	ND	ND	↔	Lefevre et al (2000)
Artemether	Healthy Thai volunteers (all M) Age: 21–28 years Wt: 45–70 kg	Open label Prospective Randomized Cross over	8	100 mg orally × 1	300 mg orally × 1	Pyrimethamine	↔	↑(44 %)	ND	↔	↓(15 %)	↔	↔	Tan-ariya et al. (1998)
Artemisinin	Healthy Vietnamese males Age: 21–45 years old Wt: 44–73 kg	Open label Prospective Randomized	10	100 mg orally × 1	500 mg orally × 1	Artesunate (dihydroartemisinin)	↑(193 %)	↑(69 %)	ND	ND	ND	↓(66 %)	↑(196 %)	Zhang et al. (2001)
Artesunate	Healthy (African, 10 M) Age: 24.4 years (mean) Wt: 67.3 kg (mean)	Randomized Prospective Cross over	13	4 mg/kg × 1 orally	10 mg/kg × 1 orally	Amodiaquine	↔	↔	ND	↔	↔	↔	↔	Orrell et al. (2008)
Artesunate	Healthy (African, 10 M) Age: 24.4 years (mean) Wt: 67.3 kg (mean)	Randomized Prospective Cross over	13	4 mg/kg × 1 orally	10 mg/kg × 1 orally	Amodiaquine (desethylamodiaquine)	↓(65 %)	↔	ND	↓(60 %)	↔	↑(164 %)	↔	Orrell et al. (2008)

Artesunate	Healthy (Karen, 8 M) Age: 33 years (median) Wt: 53 kg (median)	Open label Prospective Randomized Cross over	12	1,000 mg atovaquone + 400 mg proguanil orally × 3 doses	250 mg orally × 3 doses	Atovaquone	↔	↔	↔	↔	↔	↔	↔	van Vugt et al. (1999)
Artesunate	Healthy (Karen, 8 M) Age: 33 years (median) Wt: 53 kg (median)	Open label Prospective Randomized Cross over	12	1,000 mg atovaquone + 400 mg proguanil orally × 3 doses	250 mg orally × 3 doses	Proguanil	↔	↔	↔	↔	↔	↔	↔	van Vugt et al. (1999)
Artesunate	Healthy (Karen, 8 M) Age: 33 years (median) Wt: 53 kg (median)	Open label Prospective Randomized Cross over	12	1,000 mg atovaquone + 400 mg proguanil orally × 3 doses	250 mg orally × 3 doses	Proguanil (cycloquanil)	↔	↔	↔	↔	↔	↔	↔	van Vugt et al. (1999)
Artesunate	Thai subjects with acute, uncomplicated falciparum malaria	Open label Prospective Randomized Parallel group	8 (vs. 12 in control group)	750 mg orally × 1 then 500 mg orally 6 h later	200 mg orally × 1	Mefloquine	↔	↔	ND	↔	↑(27 %)	↑(163 %)	↔	Karbwang et al. (1994)
Artesunate	Healthy Vietnamese males Age: 21–45 years old Wt: 44–73 kg	Open label Prospective Randomized	10	500 mg orally × 1	100 mg orally × 1	Artemisinin	↓(33 %)	↓(25 %)	ND	ND		↑(49 %)	↔	Zhang et al. (2001)
Atovaquone	Thai patients with acute falciparum malaria infection	Open label Prospective Parallel group	N = 4 (control) N = 12 (combination)	200 mg orally twice daily for 3 days	500 mg orally twice daily × 3 days	Proguanil	↔	ND	ND	ND	ND	↔	↔	Edstein et al. (1996)
Atovaquone	Healthy (Caucasian, 9 M) Age: 26 years (median) Wt: 62.6 kg (median)	Open label Prospective Randomized Cross over	18	400 mg orally daily × 3 days (steady-state)	1,000 mg orally daily for 3 days	Proguanil	↔	↓(7 %)	ND	↔	↔	↔	↔	Gillotin et al. (1999)

(continued)

Table 6.1 (continued)

	Population	Design	N	Effect drug dosing	Affect drug dosing	Effects of antimalarials on antimalarial /metabolite PK								Reference
t						Analyte	AUC	Cmax	Cmin	Tmax	Vd/F	CL/F	t1/2	
Atovaquone	Healthy (Caucasian, 9 M) Age: 26 years (median) Wt: 62.6 kg (median)	Open label Prospective Randomized Cross over	18	400 mg orally daily × 3 days (steady-state)	1,000 mg orally daily for 3 days	Proguanil (cycloguanil)	↔	↔	ND	↔	ND	ND	↔	Gillotin et al. (1999)
Chloroquine	Healthy (all M) Age: 23.4 ± 3.7 years Wt: 72.7 ± 7.2 kg None poor metabolizers	Open label Prospective Cross over	14	Cocktail of caffeine (100 mg), mephenytoin (100 mg), debrisoquine (10 mg), chlorzoxazone (250 mg), and dapsone (100 mg)	250 mg orally daily × 1 and 7 days	Dapsone	ND (see text)	ND	ND	ND	ND	ND	ND	Adedoyin et al. (1998)
Chloroquine	Healthy volunteers Age: 18–55 years Wt: > 60 kg	Prospective Randomized Double blind Parallel group	20	900 mg orally daily × 2 days	600 mg orally daily × 2 days, then 300 mg orally × 1	Tafenoquine	↔	↔	ND	ND	ND	ND	↔	Miller et al. (2013)
Chloroquine	Healthy volunteers	Open label Prospective Randomized Parallel groups	8	1,500 mg/75 mg orally × 1	600 mg orally × 1	Pyrimethamine	↔	↔	ND	↔	↔	↔	↔	Obua et al. (2006)
Chloroquine	Healthy volunteers	Open label Prospective Randomized Parallel groups	8	1,500 mg/75 mg orally × 1	600 mg orally × 1	Sulfadoxine	↔	↔	ND	↔	↔	↔	↔	Obua et al. (2006)

Dapsone	Healthy volunteers	Open label Prospective Cross over	7	25 mg orally × 1	100 mg orally × 1	Pyrimethamine	ND	↔	ND	ND	↔	ND	↔	Ahmad and Rogers (1980)
Dihydroartemisinin	Healthy Thai male volunteers Age: 23–28 years old Wt: 51–57 kg	Open label Prospective Randomized Cross over	10	750 mg orally × 1	300 mg orally × 1	Mefloquine	↔	↔	ND	↔	ND	ND	↔	Na-Bangchang et al. (1999)
Mefloquine	Healthy Thai volunteers Age: 21–38 years Wt: 53–65 kg	Open label Prospective Cross over	9	45 mg orally × 1	10 mg/kg orally × 1	Primaquine	ND	↔	ND	↔	ND	ND	↔	Edwards et al. (1993)
Mefloquine	Healthy Thai volunteers Age: 21–38 years Wt: 53–65 kg	Open label Prospective Cross over	9	45 mg orally × 1	10 mg/kg orally × 1	Primaquine (carboxyprimaquine)	↔	↔	ND	↔	ND	ND	ND	Edwards et al. (1993)
Mefloquine	Healthy male Thai volunteers Age: 20–29 years old Wt: 49–57 kg	Prospective Open label Cross over	8	300 mg orally × 1	750 mg orally × 1	Artemether	↔	↔	ND	↔	↔	↔	↔	Na-Bangchang et al. (2000)
Mefloquine	Healthy male Thai volunteers Age: 20–29 years old Wt: 49–57 kg	Prospective Open label Cross over	8	300 mg orally × 1	750 mg orally × 1	Artemether (dihydroartemisinin)	↔	↔	ND	↔	ND	ND	↔	Na-Bangchang et al. (2000)
Mefloquine	Healthy male Thai volunteers Age: 24–47 years Wt: 50–65 kg	Open label Prospective Randomized Cross over	7	600 mg orally × 1	750 mg orally × 1	Quinine	↔	↔	ND	↔	↔	↔	↔	Na-Bangchang et al. (1999)
Mefloquine	Patients with symptomatic plasmodium falciparum malaria	Open label Prospective Randomized Parallel group	18 vs. 20 (control)	500 mg orally × 2, then 250 mg twice daily for 4 days (control)—total 3 g 500 mg orally, 750 mg orally, then 250 mg 3 times daily for 1 day—total 2 g (treatment group)	250 mg orally 3 times daily × 1 day	Artemisinin	Note different dose between control vs. treatment ↑(38 %)	↔	ND	↔	↓(38 %)	↓(38 %)	↔	Alin et al. (1996)

(continued)

Table 6.1 (continued)

	Population	Design	N	Effect drug dosing	Affect drug dosing	Effects of antimalarials on antimalarial /metabolite PK							Reference
t						Analyte	AUC	Cmax	Cmin	Tmax	Vd/F	CL/F	t1/2	
Mefloquine	Healthy subjects Age: 33.7 years (mean) Wt: 73.6 kg	Open label Prospective Randomized Parallel group	14	80 mg artemether/ 480 mg lumefantrine orally ever 12 h × 6 doses	1,000 mg orally divided in 3 doses over 12 h	Artemether (after single dose)	↔	↔	ND	↔	ND	ND	↔	Lefevre et al. (2000)
Mefloquine	Healthy subjects Age: 33.7 years (mean) Wt: 73.6 kg	Open label Prospective Randomized Parallel group	14	80 mg artemether/ 480 mg lumefantrine orally every 12 h × 6 doses	1,000 mg orally divided in 3 doses over 12 h	Artemether (after multiple doses)	↔	↔	ND	↔	ND	ND	↔	Lefevre et al. (2000)
Mefloquine	Healthy subjects Age: 33.7 years (mean) Wt: 73.6 kg	Open label Prospective Randomized Parallel group	14	80 mg artemether/ 480 mg lumefantrine orally every 12 h × 6 doses	1,000 mg orally divided in 3 doses over 12 h	Dihydroartemisinin (after single dose)	↔	↔	ND	↔	ND	ND	↔	Lefevre et al. (2000)
Mefloquine	Healthy subjects Age: 33.7 years (mean) Wt: 73.6 kg	Open label Prospective Randomized Parallel group	14	80 mg artemether/ 480 mg lumefantrine orally every 12 h × 6 doses	1,000 mg orally divided in 3 doses over 12 h	Dihydroartemisinin (after multiple doses)	↔	↔	ND	↔	ND	ND	↔	Lefevre et al. (2000)
Mefloquine	Healthy subjects Age: 33.7 years (mean) Wt: 73.6 kg	Open label Prospective Randomized Parallel group	14	80 mg artemether/ 480 mg lumefantrine orally every 12 h × 6 doses	1,000 mg orally divided in 3 doses over 12 h	Lumefantrine	↓(44 %)	↓(29 %)	ND	↔	ND	ND	↔	Lefevre et al. (2000)

Mefloquine	Healthy Thai male volunteers Age: 23–28 years old Wt: 51–57 kg	Open label Prospective Randomized Cross over	10	300 mg orally × 1	750 mg orally × 1	Dihydroartemisinin	↔	↔	ND	↔	ND	ND	↔	Na-Bangchang et al. (1999)
Mefloquine	Healthy male volunteers Age: 28.9 (mean) Wt: 77 kg	Open label Prospective Cross over	20	200 mg orally daily × 3	250 mg orally daily × 3	Artesunate (day 1)	ND	↔	ND	↔	ND	ND	ND	Davis et al. (2007)
Mefloquine	Healthy male volunteers Age: 28.9 (mean) Wt: 77 kg	Open label Prospective Cross over	20	200 mg orally daily × 3	250 mg orally daily × 3	Dihydroartemisnin (day 1)	↔	↔	ND	↔	↔	↔	↔	Davis et al. (2007)
Mefloquine	Healthy male volunteers Age: 28.9 (mean) Wt: 77 kg	Open label Prospective Cross over	20	200 mg orally daily × 3	250 mg orally daily × 3	Artesunate (day 3)	ND	↔	ND	↔	ND	ND	ND	Davis et al. (2007)
Mefloquine	Healthy male volunteers Age: 28.9 (mean) Wt: 77 kg	Open label Prospective Cross over	20	200 mg orally daily × 3	250 mg orally daily × 3	Dihydroartemisinin (day 3)	↔	↔	ND	↔	↔	↔	↔	Davis et al. (2007)
Primaquine	Patients with acute falciparum malaria	Open label Prospective Parallel control	14	750 mg orally × 1	45 mg orally × 1	Mefloquine	↔	↔	ND	↔	↔	↔	↔	Karbwang et al. (1990)
Primaquine	Healthy Thai male volunteers Age: 25–52 years Wt: 47–64 kg	Open label Prospective Randomized Cross over	8	750 mg orally × 1	45 mg orally × 1	Mefloquine	↔	↔	ND	↔	↔	↔	↔	Karbwang et al. (1992)
Primaquine	Healthy male Thai volunteers Age: 20–29 years old Wt: 49–57 kg	Prospective Open label Cross over	8	300 mg orally × 1	45 mg orally × 1	Artemether	↔	↔	ND	↔	↔	↔	↔	Na-Bangchang et al. (2000)
Primaquine	Healthy male Thai volunteers Age: 20–29 years old Wt: 49–57 kg	Prospective Open label Cross over	8	300 mg orally × 1	45 mg orally × 1	Artemether (dihydroartemisinin)	↔	↔	ND	↔	ND	ND	↔	Na-Bangchang et al. (2000)

(continued)

Table 6.1 (continued)

	Population	Design	N	Effect drug dosing	Affect drug dosing	Effects of antimalarials on antimalarial /metabolite PK								Reference
t						Analyte	AUC	Cmax	Cmin	Tmax	Vd/F	CL/F	t1/2	
Proguanil	Healthy (Caucasian, 9 M) Age: 26 years (median) Wt: 62.6 kg (median)	Open label Prospective Randomized Cross over	18	1,000 mg orally daily for 3 days	400 mg orally daily × 3 days (steady-state)	Atovaquone	↔	↑(9 %)	ND	↔	ND	ND	↔	Gillotin et al. (1999)
Pyrimethamine	Healthy volunteers	Open label Prospective Cross over	7	100 mg orally × 1	25 mg orally × 1	Dapsone	ND	↓(17 %)	ND	ND	↑(26 %)	ND	↔	Ahmad and Rogers (1980)
Pyrimethamine	Healthy Thai volunteers (all M) Age: 21–28 years Wt: 45–70 kg	Open label Prospective Randomized Cross over	8	300 mg orally × 1	100 mg orally × 1	Artemether	↔	↔	ND	↔	↔	↔	↔	Tan-ariya et al. (1998)
Pyrimethamine	Healthy Thai volunteers (all M) Age: 21–28 years Wt: 45–70 kg	Open label Prospective Randomized Cross over	8	300 mg orally × 1	100 mg orally × 1	Artemether (dihydroartemisinin)	↔	↔	ND	↔	ND	ND	↔	Tan-ariya et al. (1998)
Quinidine	Healthy male volunteers of Dutch ethnicity Age: 19–26 years old Wt: 65–90 kg	Open label Prospective Cross over	7	100 mg orally × 1	50 mg orally × 1	Artemether	↔	↔	ND	↔	↔	ND	↔	van Agtmael et al. (1998)
Quinidine	Healthy male volunteers of Dutch ethnicity Age: 19–26 years old Wt: 65–90 kg	Open label Prospective Cross over	7	100 mg orally × 1	50 mg orally × 1	Artemether (dihydroartemisinin)	↔	↔	ND	↔	↔	ND	↔	van Agtmael et al. (1998)
Quinine	Subjects with falciparum malaria infection (in convalescence) Age: 39.8 ± 5.7 years (mean ± SD) Wt: 51.0 ± 4.9 kg	Open label Prospective Cross over	7	45 mg orally × 1	10 mg/kg orally × 1	Primaquine	ND	↔	ND	↔	ND	ND	↔	Edwards et al. (1993)

Quinine	Subjects with falciparum malaria infection (in convalescence) Age: 39.8 ± 5.7 years (mean ± SD) Wt: 51.0 ± 4.9 kg	Open label Prospective Cross over	7	45 mg orally × 1	10 mg/kg orally × 1	Primaquine (carboxyprimaquine)	↓(49 %)	↓(43 %)	ND	↔	ND	ND	ND	Edwards et al. (1993)
Quinine	Healthy male Thai volunteers Age: 20–29 years old Wt: 49–57 kg	Prospective Open label Cross over	8	300 mg orally × 1	600 mg orally × 1	Artemether	↔	↔	ND	↔	↔	↔	↔	Na-Bangchang et al. (2000)
Quinine	Healthy male Thai volunteers Age: 20–29 years old Wt: 49–57 kg	Prospective Open label Cross over	8	300 mg orally × 1	600 mg orally × 1	Artemether (dihydroartemisinin)	↔	↔	ND	↔	ND	ND	↔	Na-Bangchang et al. (2000)
Quinine	Healthy male volunteers Age: 19–50 years old Wt: 54.5–90.6 kg	Prospective Randomized Double blind Parallel group	14	80 mg/480 mg (artemether/lumefantrine) orally × 6 doses over 60 h	10 mg/kg iv over 2 h × 1	Artemether	↓(46 %)	↔	ND	↔	ND	ND	↔	Lefevre et al. (2002)
Quinine	Healthy male volunteers Age: 19–50 years old Wt: 54.5–90.6 kg	Prospective Randomized Double blind Parallel group	14	80 mg/480 mg (artemether/lumefantrine) orally × 6 doses over 60 h	10 mg/kg iv over 2 h × 1	Artemether (dihydroartemisinin)	↓(37 %)	↔	ND	↔	ND	ND	↔	Lefevre et al. (2002)
Quinine	Healthy male volunteers Age: 19–50 years old Wt: 54.5–90.6 kg	Prospective Randomized Double blind Parallel group	14	80 mg/480 mg (artemether/lumefantrine) orally × 6 doses over 60 h	10 mg/kg iv over 2 h × 1	Lumefantrine	↔	↔	ND	↔	ND	ND	↔	Lefevre et al. (2002)

(continued)

Table 6.1 (continued)

	Population	Design	N	Effect drug dosing	Affect drug dosing	Effects of antimalarials on antimalarial /metabolite PK								Reference
t						Analyte	AUC	Cmax	Cmin	Tmax	Vd/F	CL/F	t1/2	
Sulfadoxine/ pyrimethamine	Healthy male Thai volunteers Age: 20–40 years	Open label Prospective Cross over	12	250 mg orally × 1	Sulfadoxine (1,500 mg)/ pyrimethamine (25 mg) orally × 1	Mefloquine	↔	↔	ND	↔	↔	ND	↔	Karbwang et al. (1987)
Sulfadoxine/ pyrimethamine	Healthy female Thai volunteers Age: 20–40 years	Open label Prospective Cross over	12	250 mg orally × 1	Sulfadoxine (1,500 mg)/ pyrimethamine (25 mg) orally × 1	Mefloquine	↔	↔	ND	↓(52 %)	↔	ND	↔	Karbwang et al. (1987)
Sulfadoxine/ pyrimethamine	Patients with acute falciparum malaria	Open label Prospective Parallel control	16	750 mg orally × 1	Sulfadoxine (1,500 mg)/ pyrimethamine (25 mg) orally × 1	Mefloquine	↔	↔	ND	↔	↔	↔	↔	Karbwang et al. (1990)
Sulfadoxine/ pyrimethamine + primaquine	Patients with acute falciparum malaria	Open label Prospective Parallel control	14	750 mg orally × 1	Sulfadoxine (1,500 mg)/ pyrimethamine (25 mg) and primaquine (45 mg) orally × 1	Mefloquine	↔	↔	ND	↔	↔	↔	↔	Karbwang et al. (1990)
Sulfadoxine/ pyrimethamine	Healthy volunteers	Open label Prospective Randomized Parallel group	8	600 mg orally × 1	1,500 mg/ 75 mg orally × 1	Chloroquine	↔	↔	ND	↔	↔	↔	↔	Obua et al. (2006)
Tafenoquine	Healthy volunteers Age: 18–55 years Wt: > 60 kg	Prospective Randomized Double blind Parallel group	20	600 mg orally daily × 2 days, then 300 mg orally × 1	900 mg orally daily × 2 days	Chloroquine	↔	↔	ND	ND	ND	ND	↔	Miller et al. (2013)

Tafenoquine	Healthy volunteers Age: 18–55 years Wt: > 60 kg	Prospective Randomized Double blind Parallel group	20	600 mg orally daily × 2 days, then 300 mg orally × 1	900 mg orally daily × 2 days	Chloroquine (desethylchloroquine)	↔	↔	ND	ND	ND	ND	↔	Miller et al. (2013)

AUC area under the plasma concentration-time curve, *CL/F* apparent oral clearance, *Cmax* maximal concentration, *Cmin* minimal concentration, iv *M* male, *ND* data not available, *t1/2* half-life, *PK* pharmacokinetics, *Tmax* time to reach maximum concentration, *Vd/F* apparent volume of distribution, *Wt* weight, ↔ no significant change

of mefloquine, quinine, or primaquine as evident by comparable Cmax (1,420 [929–1,870] vs. 1,375 [980–1,789]; 3,140 [1,960–4,500] vs. 3,270 [2,050–4,610]; and 197 [165–250] vs. 186 [152–225] ng/mL, median [95 % CI]), AUC (426 [250–638] vs. 452 [262–550]; 58,850 [31,500–100,000] vs. 70,850 [26,700–10,900]; 1,505 [1,173–1,943] vs. 1,488 [1,217–1,908] ng h/mL), Tmax (4 [3–12] vs. 6 [2–24]; 2.8 [1.3–4] vs. 2.8 [2–4]; 2.5 [2–2.5] vs. 0.2 [0.1–0.7] h), t1/2 (1.8 [1.2–3.1] vs. 2.2 [1.11–3.3]; 0.7 [0.4–6.3] vs. 0.8 [0.3–1.9]; 1.8 [1.2–6.5] vs. 4.0 [1.0–6.9] h), Vd/F (16.5 [14.4–22.8] vs.15.3 [12.8–22.6]; 3.2 [2.0–5.0] vs. 3.1 [2.4–4.7]; 26.1 [14.8–32.8] vs. 25.3 [18.0–32.9] L/kg), and CL/F (0.4 [0.4–1.0] vs. 0.5 [0.4–0.9]; 3.1 [1.8–5.8] vs. 2.8 [1.7–6.8]; and 62.8 [45.1–76.1] vs. 65.2 [47.0–73.4] mL/min/kg) in combination with artemether compared to each antimalarial alone, respectively. These findings are supported by the lack of known inhibitory effects by artemether toward the metabolism of these antimalarials; however, the negative findings should be interpreted in the context of the small sample size and single-dose design.

Lefevre et al. (2002) studied the pharmacokinetic interaction between artemether/lumefantrine (given as consecutive oral doses 80 mg/480 mg over 60 h) and quinine (10 mg/kg iv single dose) in healthy male volunteers, using a prospective, randomized, double-blinded, parallel group design ($n = 14$/group). Artemether/lumefantrine did not significantly affect the AUC (52.6 ± 13.2 vs. 55.7 ± 13.0 ng h/mL), Cmax ($4{,}060 \pm 62.0$ vs. $4{,}090 \pm 452$ ng/mL), Tmax (2.0 [2.0–2.0] vs. 2.0 [2.0–2.0] h, median [range]), and t1/2 (10.4 ± 1.7 vs. 9.2 ± 1.5 h) of quinine when given in combination compared to quinine alone. These findings are consistent with those reported by Na-Bangchang et al. (2000) which also demonstrated a general lack of drug interaction between quinine and artemether/lumefantrine despite these agents sharing common metabolic (i.e. CYP3A4) pathways.

Na-Bangchang et al. (1995) examined the effect of artemether (single oral dose of 300 mg) on the disposition of mefloquine (single oral dose of 750 mg) in patients of Thai ethnicity diagnosed with uncomplicated falciparum malaria ($n = 10$ vs. 17 control), using a prospective, open label, parallel group design. Artemether, administered 24 h prior, significantly decreased the Cmax (1,290 [827–2,619] vs. 1,820 [1,283–2,531] ng/mL, median [range]) and AUC_{∞} (11.11 [6–20.96] vs. 15.29 [9.3–36.71] μg day/mL), increased the Tmax (14 [5–24] vs. 6 [4–16] h), but had no effect on the t1/2 (11.1 [6.8–14.3] vs. 13.4 [10.5–19.1] h) of mefloquine compared to the mefloquine only control group, respectively. No other pharmacokinetic parameters were reported by the authors. The decreased exposure of mefloquine in the presence of artemether suggests the possibilities of a drug interaction through altered absorption or clearance. Because absorption characteristics were not reported, it is difficult to ascribe the interaction to this pharmacokinetic process. On the other hand, artemether, a substrate and an autoinducer of CYP3A4 (German and Aweeka 2008; van Agtmael et al. 1999), may have increased the intrinsic clearance of mefloquine, which is known to be metabolized by the same isoenzyme. More experiments are needed to confirm this hypothesis since the t1/2 remained unchanged and clearance parameters were not reported. Despite reduced

mefloquine exposure, however, there was a significant enhancement of parasite clearance in the combination group compared to controls taking mefloquine alone, suggesting a disconnect between pharmacokinetics and pharmacodynamics effects. No significant increases in adverse drug events were reported in the combinations group, but these observations should be reproduced under steady-state conditions.

The pharmacokinetic interaction between mefloquine (1,000 mg orally divided in 3 doses over 12 h) and artemether/lumefantrine (80 mg/480 mg orally every 12 h for 6 doses) was examined by Lefevre et al. (2000) in healthy volunteers, using an open label, prospective, parallel group design ($n = 14$ in each group). Steady-state artemether/lumefantrine did not have a significant effect on the Cmax (973 ± 315 vs. $1{,}000 \pm 266$ ng/mL, mean $\pm$ SD), Tmax (18 [14–32] vs. 23 [10–38] h), AUC_{∞} (412 ± 142 vs. 375 ± 125 μg h/mL), and t1/2 (385 ± 141 vs. 427 ± 198 h) of mefloquine when administered in combination compared to mefloquine alone, respectively. The lack of apparent pharmacokinetics interaction between artemether/lumefantrine and mefloquine in this study is inconsistent with that reported by Na-Bangchang et al. (1995), but there are design differences between these two studies (i.e. healthy volunteers vs. patients; single dose vs. steady-state) that may have resulted in these discrepancies. Mefloquine, artemether, and lumefantrine are all metabolized primarily by CYP3A4 (German and Aweeka 2008; Fontaine et al. 2000) and artemether is also an autoinducer of CYP3A4 (van Agtmael et al. 1999); these characteristics impart some degree of complexity to the molecular basis of the pharmacokinetic interaction between these drugs. Opposing inductive and inhibitory effects toward the same isoenzyme may be hypothesized to explain the lack of pharmacokinetic interaction, but one should also take into account the very large variability and the relatively small sample used.

Tan-ariya et al. (1998) studied the pharmacokinetic interaction between pyrimethamine (single oral dose of 100 mg) and artemether (single oral dose of 300 mg) in healthy male volunteers of Thai origin ($n = 8$), using an open label, prospective, cross over design. Artemether significantly increased Cmax (1,180 [631–1,500] vs. 818 [676–1,190] ng/mL, median [range]) and decreased Vd/F (2.56 [1.88–4.16] vs. 3 [1.83–4.02] L/kg), but had little effect on Tmax (1.25 [0.5–1.5] vs. 1.5 [1–4] h), AUC (75.7 [49.1–79] vs. 63.8 [43.9–86.8] μg h/mL), t1/2 (77 [49.7–90.5] vs. 67.1 [58.6–106] h), and CL/F (22.8 [21.2–34.2] vs. 28.5 [16.7–31.1] mL/min/kg), when used in combination compared to pyrimethamine alone, respectively. The magnitude of the changes (in Cmax and Vd/F) is considered small and difficult to explain by the known metabolic properties of pyrimethamine: it is not extensively metabolized nor is it a substrate of any major CYP450 enzymes (Li et al. 2003). The authors hypothesize that protein binding displacement by artemether may explain the increased Cmax, but this would contradict the reduced volume of distribution also observed in this study. One should interpret these data in the context of the small sample size and large variability. It is also not known if these observations can be observed under steady-state (i.e. clinical) dosing conditions.

6.3 Effects of Artemisinin on the Pharmacokinetics of Antimalarials

Zhang et al. (2001) examined the pharmacokinetic interaction between single oral doses of artesunate (100 mg) and artemisinin (500 mg) in healthy Vietnamese male volunteers (n = 10) using an open label, prospective, randomized design. Artemisinin significantly increased the AUC_{∞} (8,121 [5,534–11,917] vs. 2,765 [1,637–4,670] nmol h/L, mean [95 % CI]), Cmax (2,821 [1,968–4,043] vs. 1,664 [999–2,772] nmol/L), t1/2 (1.63 [1.34–1.99] vs. 0.55 [0.44–0.70] h), but decreased the Cl/F (32 [22–47] vs. 94 [56–159] L/h) of the major metabolite of artesunate, dihydroartemisinin, in combination treatment compared to artesunate alone, respectively. Although dihydroartemisinin pharmacokinetic parameters were also determined after 5 days of continuous artesunate administration, there lacked a control for comparison. Artesunate is converted primarily by CYP2A6 to dihydroartemisinin (Li et al. 2003), which is further conjugated by UGT1A9 and UGT2B7 (Ilett et al. 2002). These findings may suggest that artemisinin had an inhibitory effect toward the glucuronidation of dihydroartemisinin, although the molecular basis for this interaction needs to be verified (i.e. by using an established in vitro system to test the inhibition UGT1A9 and UGT2B7 probe substrates). Unfortunately, the pharmacokinetics of artesunate was not studied which may have provided further mechanistic insights into the interaction.

6.4 Effects of Artesunate on the Pharmacokinetics of Antimalarials

Orrell et al. (2008) examined the pharmacokinetic interaction between artesunate and amodiaquine in healthy volunteers of African descent. Using a randomized, prospective, and crossover design, subjects received either artesunate (4 mg/kg), amodiaquine (10 mg/kg), or the combination, as single oral doses. The study also determined the concentrations of the major metabolite for amodiaquine (desethylamodiaquine). The major findings from these experiments were significantly reduced desethylamodiaquine AUC (12,041 ± 3,480 vs. 8,437 ± 4,009 ng h/mL, mean ± SEM) and Tmax (3.68 ± 1.85 vs. 2.18 ± 1.03 h), and increased Cl/F (768 ± 252 vs. 1,330 ± 735 L/min) for subjects given amodiaquine alone or in combination with artesunate, respectively. Although there were trends toward a decrease in day 7 desethylamodiaquine concentrations, the effect was not significant. Likewise, only trends toward decreases in the AUC, Cmax, Tmax and t1/2 of the parent artesunate in the presence of amodiaquine were observed. Based on in vitro experiments, CYP2C8 is known to be the primary isoenzyme responsible for the metabolism of amodiaquine (Li et al. 2002, 2003) but it remains to be determined if artesunate or its major metabolite, dihydroartemisinin, has inhibitory effects toward CYP2C8. The metabolism of desethylamodiaquine could also be

affected by artesunate, but the metabolic pathways for this major metabolite needs to be investigated further. More importantly, it is not known whether the altered pharmacokinetic characteristics of desethylamodiaquine, which has pharmacological activity, is translated to a reduced clinical effect (which was not determined in this study). As discussed above, the combination of artesunate and amodiaquine has generally been documented to be more efficacious in malaria treatment than amodiaquine or artesunate alone. Similar limitations of large variability and small sample size is described for this study, and these pharmacokinetic perturbations should ideally be confirmed in the target population under clinical (i.e. steady-state) dosing conditions.

Using a prospective, randomized, cross over design, van Vugt et al. (1999) studied the effect of artesunate (250 mg orally × 3 doses) on the pharmacokinetics of atovaquone and proguanil (given in a fixed combination of 1,000 mg/400 mg orally × 3 doses) in 12 healthy adult Karen volunteers. Artesunate did not affect the pharmacokinetics of atovaquone as evident by comparable Cmax (13.27 ± 6.14 vs. 13.02 ± 8.28 μg/mL, mean ± SEM), Cmin (7.66 ± 4.49 vs. 6.75 ± 3.44 μg/mL), Tmax (5.5 ± 4.4 vs. 5.7 ± 4.0 h), t1/2 (38.5 ± 15.6 vs. 42.2 ± 22.0 h), AUC_{∞} (293 ± 163 vs. 265 ± 120 μg h/mL), Cl/F (93 ± 61 vs. 90 ± 47 mL/h/kg), and Vd/F (4.7 ± 3.3 vs. 4.9 ± 3.0 L/kg) in subjects receiving the combination compared to atovaquone with proguanil alone. There was very large variability; thus these negative findings should be interpreted with caution given the relatively small sample size. Because atovaquone is not extensively metabolized, the lack of interaction with artesunate may be reasonable from a mechanistic point of view.

Artesunate did not affect the pharmacokinetics of proguanil as evident by comparable Cmax (751 ± 242 vs. 742 ± 220 ng/mL, mean ± SEM), Cmin (193 ± 59 vs. 240 ± 63 ng/mL), Tmax (5.2 ± 1.9 vs. 4.4 ± 1.2 h), t1/2 (14.3 ± 2.6 vs. 14.4 ± 2.7 h), AUC_{∞} (9,428 ± 2,811 vs. 10,425 ± 3,290 ng h/mL), Cl/F (764 ± 203 vs. 710 ± 250 mL/h/kg), and Vd/F (15.8 ± 5.5 vs. 14.5 ± 4.8 L/kg) in subjects receiving the combination compared to atovaquone with proguanil alone. Similar findings of no pharmacokinetic interactions were observed for the metabolite cycloguanil as evident by comparable Cmax (67 ± 72 vs. 60 ± 76 ng/mL, mean ± SEM), Cmin (16 ± 9 vs. 21 ± 25 ng/mL), Tmax (6.4 ± 3.1 vs. 6.4 ± 2.3 h), t1/2 (15.6 ± 3.9 vs. 17.7 ± 2.9 h), and AUC_{∞} (1,810 ± 1,308 vs. 1,748 ± 1,639 ng h/mL) in subjects receiving the combination compared to atovaquone with proguanil alone, respectively. These observations are supported by the fact that proguanil is metabolized by CYP3A (Birkett et al. 1994), CYP2C19 (Coller et al. 1999), and CYP1A2 (Coller et al. 1999), none of which were inhibited by artesunate as shown by Bapiro et al. (2001) in vitro. Again, one should interpret these negative findings in light of the large variability and the relatively small sample size.

The effects of artesunate (200 mg orally × 1) on the pharmacokinetics of mefloquine (750 mg orally × 1 followed by 500 mg orally 6 h later) were studied by Karbwang et al. (1994) in patients diagnosed with acute, uncomplicated falciparum malaria (n = 20 total), using a prospective, open label, randomized, parallel group design. Artesunate increased the Cl/F (2.9 ± 6.6 vs. 1.1 ± 0.50 mL/min/kg,

mean ± SD) and Vd/F (31.8 ± 5.1 vs. 25.0 ± 6.0 L/kg) but did not change the Cmax (1,623 ± 388 vs. 2,212 ± 513 ng/mL), Tmax (15.0 ± 3.0 vs. 20.3 ± 5.2 h), AUC (12.8 (SD not determined) vs. 17.2 ± 6.4 μg d/mL), and t1/2 (11.0 ± 7.0 vs. 11.9 ± 2.7 days) of mefloquine when administered in combination compared to mefloquine alone, respectively. The lack of change in mefloquine exposure in the presence of artesunate is consistent with the known metabolic properties of the two agents: that mefloquine is primarily metabolized by CYP3A4 (Fontaine et al. 2000) and that artesunate has little inhibitory effects toward this isoenzyme (Bapiro et al. 2001). On the other hand, increased volume of distribution and clearance were attributed by the authors to protein binding displacement by artesunate which hypothetically increased the free fraction and rate of clearance of mefloquine. Despite the lack of a significant pharmacokinetic interaction, the combination of artesunate and mefloquine resulted in a significant shortened fever and parasite clearance times, and little difference in adverse effects.

Zhang et al. (2001) examined the pharmacokinetic interaction between single oral doses of artesunate (100 mg) and artemisinin (500 mg) in healthy Vietnamese male volunteers (n = 10) using an open label, prospective, randomized design. Significantly decreased AUC_{∞} (5,763 [4,813–6,901] vs. 8,555 [6,212–11,781] nmol h/L, mean [95 % CI]), Cmax (1,803 [1,413–2,299] vs. 2,408 [1,824–3,179] nmol/L) but increased Cl/F (308 [257–368] vs. 207 [151–285] L/h) of artemisinin were observed when subjects were given the combination of artemisinin and artesunate. These findings were attributed by the authors to the autoinduction effects of artemisinin itself, rather than any effects by artesunate which is not known to induce the CYP450 enzymes responsible for the metabolism of artemisinin. The experimental design of the study, however, did not allow the verification of autoinduction which remains to be further tested.

6.5 Effects of Atovaquone on the Pharmacokinetics of Antimalarials

Edstein et al. (1996) examined the effect of atovaquone (500 mg orally twice daily for 3 days) on the pharmacokinetics of proguanil (200 mg orally twice daily for 3 days) in patients of Thai ethnicity infected with acute falciparum malarial infection (n = 12 in combination vs. n = 4 control patients on proguanil alone). Atovaquone did not affect the Cl/F (0.95 [0.73–1.32] vs. 1.25 [0.99–1.45] L/h/kg, median [range]), t1/2 (13.6 [9.1–17.6] vs. 14.2 [9.3–16.8] h), and AUC_{∞} (27.1 vs. 16.8 μg h/mL, no range provided) of proguanil, when given in combination compared to proguanil alone, respectively. The lack of pharmacokinetic interaction between atovaquone and proguanil may be explained by the fact that proguanil is predominately bioactivated by CYP2C19 (Funck-Brentano et al. 1997) and atovaquone has very little inhibitory effects toward this isoenzyme (Bapiro

et al. 2001) in humans. However, the results of this study should be interpreted in the context of small sample size, unbalanced groups, and large variability.

The effects of atovaquone (1,000 mg orally daily for 3 days) on the pharmacokinetics of steady-state proguanil (given as 400 mg orally × 3 days), the typical dosing regimen recommended for malaria treatment, was studied by Gillotin et al. (1999) in healthy volunteers (n = 18) using an open label, prospective, randomized cross over design. Similar to the lack of effect by proguanil on the pharmacokinetics of atovaquone, neither the pharmacokinetics of proguanil nor its active metabolite, cycloguanil, was affected by atovaquone. For proguanil, only the Cmax was slightly decreased (509.4 [351.3–819.9] vs. 547.6 [382.7–911.7] ng/mL, mean [range]) and no differences were observed for Tmax (3 [2–6] vs. 3 [2–4] h), AUC_{∞} (5,998 [3,551–8,361] vs. 6,437 [2,959–12,084] ng h/mL), t1/2 (14.5 [10.3–20.4] vs. 13.7 [8.6–18.3] h), Cl/F (1,146 [797–1,878] vs. 1,082 [552–2,253] mL/min), and Vd/F (1,399 [822–2,337] vs. 1,226 [790–1,763] L), for subjects taking the combination compared to proguanil alone, respectively. A lack of effect of atovaquone on cycloguanil (metabolite) pharmacokinetics was evident by similar Cmax (79.2 [5.3–194.9] vs. 82.1 [5.5–208.4] ng/mL), Tmax (6 [4–8] vs. 6 [4–8] h), AUC_{∞} (1,203 [413–2,197] vs. 1,355 [428–3,172] ng h/mL), and t1/2 (11.8 [4.9–27.0] vs. 11.1 [4.3–21.3] h), for combination treatment compared to proguanil alone, respectively. The ratio of cycloguanil and proguanil also remained the same in combination (0.21) or single (0.22) treatment, suggesting an absence of a metabolic interaction at the enzymatic level. These observations are supported by the fact that proguanil is primarily metabolized by CYP3A (Birkett et al. 1994), CYP2C19 (Coller et al. 1999), and CYP1A2 (Coller et al. 1999), none of which were inhibited by atovaquone as shown by Bapiro et al. (2001) in vitro. However, one should consider the large variabilities in all the pharmacokinetic parameters and the relatively small sample size when interpreting these negative findings.

6.6 Effects of Chloroquine on the Pharmacokinetics of Antimalarials

The effects of chloroquine on the pharmacokinetics of dapsone have been described above (Adedoyin et al. 1998). Miller et al. (2013) examined the pharmacokinetic interaction between tafenoquine (900 mg orally daily × 2), a new agent being developed for the treatment and eradication of hepatic *P. vivax*, and chloroquine (600 mg orally daily × 2, then 300 mg × 1) in healthy volunteers (n = 20), using a prospective, randomized, double blind design. Chloroquine did not affect the pharmacokinetics of tafenoquine, as evident by the similar AUC_{∞} (0.98 [0.84–1.14] ng h/mL, geometric mean ratio [90 % CI] between combination to tafenoquine alone), Cmax (1.13 [0.96–1.34] ng/mL), and t1/2 (1.06 [0.94–1.20] h). No other pharmacokinetic parameters were reported. Although there was a trend toward a transient increase in the geometric mean ratio of tafenoquine Cmax at day

2, the effect was diminished at end of the dosing regimen (day 3). The lack of pharmacokinetic interaction was translated into a lack of pharmacodynamic interaction between these agents, including a negligible effect on QT prolongation. This is a well powered study and the negative findings support, in theory, the lack of metabolism-based interaction between tafenoquine (not extensively metabolized and unlikely subjected to CYP450-mediated interaction) and chloroquine (a weak inhibitor of CYP2D6).

6.7 Effects of Dapsone on the Pharmacokinetics of Antimalarials

Ahmad and Rogers (1980) examined the pharmacokinetic interaction between dapsone (single oral 100 mg dose) and pyrimethamine (single oral 25 mg dose) in healthy volunteers ($n = 7$), using a prospective, open label, cross over design. Dapsone did not affect the absorption constant (0.72 ± 0.25 vs. 1.01 ± 0.38 h^{-1}, mean ± SD), t1/2 (83.2 ± 30.3 vs. 82.5 ± 13.6 h), Cl/F (25.8 ± 7.1 vs. 24.8 ± 3.8 mL h/kg), Vd/F (3.02 ± 0.72 vs. 2.93 ± 0.52 L/kg), and Cmax (235 ± 15 vs. 234 ± 21 ng/mL) of pyrimethamine when given in combination treatment compared to pyrimethamine alone, respectively. Because pyrimethamine is not extensively metabolized, nor is it a substrate of any major CYP450 enzymes (Li et al. 2003), the lack of drug interaction observed in this in vivo study may be explained by its inert metabolic properties. However, it is unclear if these observations are reproducible in the patient population under clinical (i.e. steady-state) dosing conditions.

6.8 Effects of Mefloquine on the Pharmacokinetics of Antimalarials

Edwards et al. (1993) studied the effects of mefloquine (single 10 mg/kg oral dose) or quinine (10 mg/kg single oral dose) on the pharmacokinetics of primaquine (single 45 mg oral dose) in healthy male volunteers ($n = 9$) or patients infected with falciparum malaria in convalescence ($n = 7$), respectively, using an open label, prospective, cross over design. Mefloquine did not change the Cmax (229 [114–503] vs. 167 [113–532] μg/L, median [range]), Tmax (3 [2–4] vs. 2 [1–4] h), Cl/F (34.0 [21.7–49.0] vs. 33.1 [17.6–49.3] L/h), or t1/2 (3.9 [1.7–13.5] vs. 6.1 [1.7–16.1] h) of primaquine, when used in combination compared to primaquine alone, respectively. Likewise, little effect from mefloquine co-administration on the pharmacokinetics of carboxyprimaquine, a major metabolite of primaquine, was observed, as evident by similar Cmax (1,035 [174–3,015] vs. 890 [553–3,634] μg/L, median [range]), Tmax (8 [2–24] vs. 6 [3–16] h), and AUC_{last} (13,471 [2,132–

17,863] vs. 12,737 [6,837–27,388] μg h/L) when comparing combination treatment to primaquine alone, respectively. In patients in convalescence from malaria infection, quinine did not change the Cmax (295 [64–308] vs. 271 [147–431] μg/L, median [range]), Tmax (2 [1.5–4] vs. 3 [1.5–4] h), Cl/F (21.3 [15.9–73.0] vs. 24.8 [12.6–48.4] L/h), or t1/2 (5.1 [1.4–11.6] vs. 3.5 [2.7–7.9] h) of primaquine, when used in combination compared to primaquine alone, respectively. On the other hand, quinine significantly decreased Cmax (343 [185–875] vs. 600 [380–1,055] μg/L, median [range]) and AUC_{last} (3,831 [2,144–15,882] vs. 7,533 [4,876–18,545] μg h/L) but had little effect on Tmax (4 [1.5–24] vs. 8 [3–24] h) of primaquine. The lack of an in vivo pharmacokinetic interaction between mefloquine and primaquine observed in this study may be explained, other than the small sample size and large variability, by the fact that mefloquine has not been known to affect the CYP450 isoenzymes responsible for the metabolism of primaquine in humans (CYP1A2 and CYP2D6 (Li et al. 2003). On the other hand, quinine is a potent inhibitor of CYP2D6 (Bapiro et al. 2001) in vitro, which may explain the significant reduction in the formation of carboxyprimaquine and a trend toward an increase in Cmax of primaquine, when quinine was co-administered to test subjects. However, other pharmacokinetic parameters (e.g. AUC of primaquine in plasma or the metabolic ratio) needed to have been determined to confirm this hypothesis.

Na-Bangchang et al. (2000) studied the pharmacokinetic interactions between single oral doses of primaquine (45 mg), mefloquine (750 mg), quinine (600 mg), and artemether (300 mg) in healthy male Thai volunteers (n = 8), using a prospective, open label, cross over design. Mefloquine, quinine, primaquine did not affect the Cmax (421 [314–498], 369 [265–560], 389 [290–490] vs. 411 [280–555] ng/mL, median [95 % CI]), AUC (1,947 [913–2,992], 1,832 [944–3,456], 1,617 [1,013–2,528] vs. 1,862 [1,032–2,696] ng h/mL), Tmax (2 [1.5–2.0], 2 [2–2], 2 [1.5–2.0] vs. 2 [1.5–2] h), t1/2 (1.3 [1–1.5], 1.1 [0.8–1.5], 1.1 [0.8–1.5] vs. 1.3 [0.9–1.4] h), Vd/F (10.6 [9.1–14.2], 12.2 [10.4–15.2], 10.5 [7.6–13.7] vs. 11.2 [8.9–13.9] L/kg), or CL/F (56.9 [30–109.4], 52.8 [25.9–106], 58.8 [35.4–98.6] vs. 51.7 [33.4–96.8] mL/min/kg) of artemether when given in combination compared to artemether alone, respectively. Similar findings were observed for the CYP3A4-catalyzed metabolite, dihydroartemisinin, where none of the co-administered antimalarials had a significant effect on any reported pharmacokinetic parameters. These findings reinforce the lack of inhibitory effects by these co-administered antimalarials toward CYP3A4, the primary enzyme responsible for the metabolism of artemether as supported by in vitro data (Bapiro et al. 2001), despite quinine and mefloquine both being substrates for the same isoenzyme (Fontaine et al. 2000; Li et al. 2003). These negative findings, however, should be interpreted in the context of the small sample size and single-dose design.

Na-Bangchang et al. (1999) studied the pharmacokinetic interaction between quinine (600 mg orally × 1) and mefloquine (750 mg orally × 1) in healthy male Thai volunteers (n = 7), using a prospective, open label, cross over design. Mefloquine had little effect on the pharmacokinetics of quinine, as evident by comparable Cmax (3,270 [2,660–4,740] vs. 3,320 ng/mL [2,870–6,600], median [range]), Tmax (2 [1.5–3] vs. 1 [1–2.5] h), AUC (55 [range not specified] vs. 53.2 [40.1–98.2] ng h/

mL), CL/F (7.65 [6.52–3.48] vs. 7.82 [3.75–10.4]), t1/2 (15.4 [8.2–19.7] vs. 12.5 [7.9–18.3] h), and Vd/F (7.8 [5.7–10.4] vs. 7.1 [4.9–11.4] L/kg) when given in combination compared to quinine alone, respectively. Because both quinine and mefloquine are metabolized primarily by CYP3A4 (Fontaine et al. 2000; Li et al. 2003), there is a metabolic basis for drug-drug interaction that was not observed in this study. These negative findings, however, should be weighted in the context of small sample size and large variability. On the other hand, the combination of quinine and mefloquine resulted in a significant increase in QT_C interval, indicating the presence of a pharmacodynamic interaction. The pharmacokinetics/pharmacodynamic interaction between quinine and mefloquine should be tested at steady state in the actual patient population.

The effects of mefloquine (250 mg orally 3 times daily for 3 doses) on the disposition of artemisinin (3 g in control vs. 2 g in combination group, in divided doses) were reported by Alin et al. (1996) in patients symptomatic with falciparum malaria ($n = 18$ vs. $n = 20$ in control), using a prospective, randomized, open label, parallel group design. Mefloquine significantly increased the AUC_{last} ($2{,}786 \pm 1{,}608$ vs. $2{,}014 \pm 1{,}359$ ng h/mL, mean ± SD) of artemisinin in combination treatment compared to artemisinin alone, respectively, despite a lower artemisinin dose in the combination group. There were also significant changes in the clearance and volume of distribution of artemisinin in the combination group but these effects are not directly comparable due to a different dose of artemisinin given in the control. No other pharmacokinetic parameters were reported by the authors. The apparent increase in the exposure of artemisinin (despite a lower dose) in the presence of mefloquine may be explained by the fact that both agents are known substrates of CYP3A4 (Fontaine et al. 2000; Li et al. 2003) and thus may compete with each other for enzyme binding sites. Because of unbalanced dosing regimens in the two comparable groups, however, definitive conclusions about this proposed interaction cannot be drawn from the data obtained in this study.

The pharmacokinetic interaction between mefloquine (1,000 mg orally divided in 3 doses over 12 h) and artemether/lumefantrine (80 mg/480 mg orally every 12 h for 6 doses) was examined by Lefevre et al. (2000) in healthy volunteers, using an open label, prospective, parallel group design ($n = 14$ in each group). Mefloquine did not have a significant effect on the Cmax (98.8 ± 43.1 vs. 72.2 ± 33.2 ng/mL, mean ± SD), Tmax (1.0 [0.5–3] vs. 2.0 [0.5–3] h), AUC_{last} (223 ± 112 vs. 204 ± 107 ng h/mL), and t1/2 (1.7 ± 1.0 vs. 1.4 ± 0.4 h) of single-dose artemether when administered in combination compared to artemether/lumefantrine alone, respectively. Likewise, mefloquine had little effect on the Cmax (28.6 ± 15.2 vs. 27.4 ± 30.9 ng/mL, mean ± SD), Tmax (2.0 [1–3] vs. 1.5 [1–4] h), and AUC_{last} (58.6 ± 48.6 vs. 63.6 ± 72.5 ng h/mL) of steady-state artemether when given as a combination compared to the control group. Similar patterns (i.e. lack of pharmacokinetic interaction) of dihydroartemisinin, the major active metabolite of artemether, from the co-administration of mefloquine were also observed after single or multiple doses of artemther/lumefantrine. The exposure of artemether was decreased and that of dihydroartemisinin increased when comparing the values from the 6^{th} to the first dose, indicative of the known autoinductive

effects of artemether on its own biotransformation. On the other hand, mefloquine significantly decreased the Cmax (20.0 ± 8.3 vs. 28.3 ± 13.6 μg/mL) and AUC_{∞} ($1{,}530 \pm 777$ vs. $2{,}730 \pm 1{,}710$ μg h/mL), but had little effect on the Tmax and t1/2 of lumefantrine when given in combination compared to the control. Mefloquine, artemether, and lumefantrine are all metabolized primarily by CYP3A4 (German and Aweeka 2008; Fontaine et al. 2000), and artemether is also an autoinducer of CYP3A4 (van Agtmael et al. 1999); these characteristics impart some degree of complexity to the molecular basis of the pharmacokinetic interaction between these drugs. The reduced exposure of lumefantrine in the presence of mefloquine has been suggested by the authors to be a decrease in bile production, but this hypothesis remains to be investigated. Because other CYP450 and UGT enzymes are known to catalyze artemether and dihydroartemisinin, it also may be possible that mefloquine could have inductive or inhibitory effects toward these other metabolic pathways. The clinical significance of reduced lumefantrine exposure remains to be determined in patients but may be insignificant given the small magnitude of the pharmacokinetic interaction and the synergistic effects from artemether co-treatment.

The pharmacokinetic interaction between dihydroartemisinin (300 mg orally for 1 dose) and mefloquine (750 mg orally for 1 dose) was studied by Na-Bangchang et al. (1999) in healthy male Thai volunteers ($n = 10$), using an open label, prospective, randomized, cross over design. Mefloquine did not affect the disposition of dihydroartemisinin, as evident by comparable Cmax (624 [394–969] vs. 653 [443–854] ng/mL, median [range]), Tmax (1.1 [1.2–2.4] vs. 1.4 [1.2–1.8] h), t1/2 (0.2 [0.11–0.22] vs. 0.2 [0.1–0.38] h), AUC (2,110 [1,122–4,770] vs. 2,120 [1,210–4,380] ng h/mL), CL/F (43.8 [20.2–79.8] vs. 43.7 [23.8–75] mL/min/kg), and Vd/F (3.25 [2.58–8.0] vs. 3.46 [2.82–5.93] L/kg) of dihydroartemisinin when given in combination compared to dihydroartemisinin alone, respectively. The lack of interaction may be explained by the known metabolic properties of these agents: that dihydroartemisinin is primarily conjugated by UGT1A9 and UGT2B7 (Ilett et al. 2002) and that mefloquine has little known effects on these phase II enzymes.

The effects of mefloquine (250 mg orally daily × 3) on the disposition of artesunate (200 mg orally daily × 3) was examined by Davis et al. (2007) in healthy male volunteers ($n = 20$), using a prospective, open label, cross over design. Mefloquine did not alter Cmax (91 [44–189] vs. 135 [58–316] μg/L, mean [range]) and Tmax (0.5 [0.3–0.7] vs. 0.6 [0.4–0.9] h) of artesunate after a single dose, or Cmax (109 [39–104] vs. 113 [44–290 μg/L], mean [range]) and Tmax (0.5 [0.3–0.7] vs. 0.6 [0.4–0.9] h) of artesunate after 3 doses, when given in combination compared to artesunate alone, respectively. Likewise, the pharmacokinetics of the major metabolite, dihydroartemisinin, was not significantly changed in the presence of mefloquine, as evident by comparable Cmax (508 [345–748] vs. 67 5 [522–873] μg/L), Tmax (1.3 [0.7–2.3] vs. 1.0 [0.6–1.8] h), AUC_{∞} (1,217 [850–1,742] vs. 1,443 [1,082–1,924] μg h/L), t1/2 (1.02 [0.90–1.94] vs. 1.14 [0.98–1.31] h), Vd/F (201 [160–243] vs. 174 [143–205] L), and CL/F (128 [116–146] vs. 106 [94–119] L/h) when given in combination compared to the first dose of artesunate alone, respectively. Similar finding of lack of pharmacokinetic interaction was observed

for dihydroartemisinin when mefloquine and artesunate were co-administered for 3 days. The lack of pharmacokinetic interaction between artesunate and mefloquine may be explained by the known metabolic properties of these agents: that artemether is primarily metabolized by CYP2A6 (Li et al. 2003), dihydroartemisinin is primarily conjugated by UGT1A9 and UGT2B7 (Ilett et al. 2002), and mefloquine has little known effects toward these enzymes.

6.9 Effects of Primaquine on the Pharmacokinetics of Antimalarials

The effects of primaquine on the pharmacokinetics of artemether have been described in the aforementioned study conducted by Na-Bangchang et al. (2000). Karbwang et al. (1990) followed up their initial study in healthy volunteers with patients infected with acute falciparum malaria (n = 14–16) and examined the effects of co-administered primaquine (45 mg orally × 1), sulfadoxine/pyrimethamine (1,500 mg/25 mg orally × 1), or sulfadoxine/pyrimethamine/primaquine (1,500 mg/25 mg/45 mg orally × 1) on the pharmacokinetics of a single oral dose of mefloquine (75 mg), using a prospective, open label, parallel control design. Despite relatively small sample sizes, the groups were relatively balanced. Primaquine did not significantly affect the pharmacokinetics of mefloquine as evident by similar Tmax (14.1 ± 8.1 vs. 16.9 ± 13.2 h, mean ± SD), Cmax (2,303 ± 854 vs. 2,690 ± 572 ng/mL), t1/2 (11.4 ± 1.3 vs. 11.7 ± 2.0 days), AUC (24.9 ± 9.9 vs. 27.0 ± 8.2 μg d/mL), Vd/F (587 ± 265 vs. 500 ± 135 L), and Cl/F (34.9 ± 13.7 vs. 30.6 ± 10.0 L/day) when given in combination compared to primaquine alone, respectively. Sulfadoxine/pyrimethamine also did not change the disposition of primaquine, as demonstrated by comparable Tmax (19.0 ± 13.3 vs. 16.9 ± 13.2 h, mean ± SD), Cmax (2,559 ± 1,107 vs. 2,690 ± 572 ng/mL), t1/2 (10.4 ± 1.9 vs. 11.7 ± 2.0 days), AUC (25.6 ± 8.7 vs. 27.0 ± 8.2 μg d/mL), Vd/F (667 ± 322 vs. 500 ± 135 L), and Cl/F (35.7 ± 14.1 vs. 30.6 ± 10.0 L/day) for the combination compared to mefloquine alone, respectively. Likewise, the combination of sulfadoxine/pyrimethamine/primaquine had little effect on the pharmacokinetics of mefloquine. These findings of no pharmacokinetic interaction may be supported by the lack of molecular basis for a metabolic interaction between these agents. Mefloquine is primarily metabolized by CYP3A isoenzymes (Fontaine et al. 2000) which is not known to be affected by the co-administered drugs examined in this study. However, the negative results should be considered in the context of the large variability and small sample sizes. Whether these observations are reproducible at steady state also remain to be determined.

The effects of a single oral dose of primaquine (45 mg) on the disposition of mefloquine (750 mg orally × 1) was further examined by Karbwang et al. (1992) in healthy mail Thai volunteers (n = 8), using an open label, prospective, randomized cross over design. Like the findings from Karbwang et al. (1990) in patients with

acute falciparum malaria, primaquine did not affect the Cmax (1,179 ± 153 vs. 1,161 ± 120 ng/mL, mean ± SD), Tmax (6.4 ± 3.6 vs. 5.6 ± 2.8 h), AUC (20.2 ± 4.8 vs. 20.0 ± 3.8 μg h/mL), t1/2 (17.0 ± 2.6 vs. 19.7 ± 3.2 h), Cl/F (0.51 ± 0.11 vs. 0.48 ± 0.07 mL/min/kg), and Vd/F (19.2 ± 4.7 vs. 19.6 ± 4.0 L/kg) of mefloquine when given in combination compared to mefloquine alone, respectively, in healthy subjects. The lack of drug interaction may be explained by the fact that mefloquine is primarily metabolized by CYP3A (Fontaine et al. 2000) and that primaquine is not known to have an inhibitory effect toward the isoenzyme.

6.10 Effects of Proguanil on the Pharmacokinetics of Antimalarials

The effects of steady-state proguanil (given as 400 mg orally × 3 days) on the pharmacokinetics of atovaquone (1,000 mg orally daily for 3 days), the typical dosing regimen recommended for malaria treatment, was studied by Gillotin et al. (1999) in healthy volunteers (n = 18) using an open label, prospective, randomized cross over design. Other than a slight, but significant increase in Cmax (11.54 [7.86–16.16] vs. 10.52 [5.99–16.43] μg/mL, mean [range]), little effect on the pharmacokinetics of atovaquone was observed, as evident by comparable Tmax (3 [2–4] vs. 3 [2–4] h), AUC_{∞} (510 [247–919] vs. 549 [267–980] μg h/mL), and t1/2 (59.0 [41.1–93.4] vs. 57.1 [35.2–115.7] h) in subjects taking the combination compared to atovaquone alone, respectively. Because the t1/2 of atovaquone was approximately 59 h, the 3-day dosing regimen used here was not reflective of steady-state conditions. Given the large variability of the data observed and the small sample, it is not clear if the elevation in Cmax is reproducible and/or has clinical relevance, as the primary focus of the study was not on pharmacodynamic effects. One can argue that the small magnitude of the increase in Cmax will unlikely have any clinically significant impact, but these observations should be reproduced and characterized in the target, malaria-infected population. The results from this study are supported by the lack of vitro interaction data between this drug pair.

6.11 Effects of Pyrimethamine on the Pharmacokinetics of Antimalarials

Ahmad and Rogers (1980) examined the pharmacokinetic interaction between dapsone (single oral 100 mg dose) and pyrimethamine (single oral 25 mg dose) in healthy volunteers (n = 7), using a prospective, open label, cross over design. Pyrimethamine did not affect the absorption constant (0.48 ± 0.18

vs. 0.61 ± 0.42 h^{-1}, mean ± SD), distribution rate constant (0.026 ± 0.004 vs. 0.026 ± 0.003 h^{-1}), t1/2 (27.2 ± 3.9 vs. 27.5 ± 3.3 h), or Cl/F (47.0 ± 7.4 vs. 38.4 ± 10.9 mL/h/kg) but significantly increased Vd/F (1.93 ± 0.34 vs. 1.53 ± 0.52 L/kg) and decreased Cmax ($1{,}550 \pm 110$ vs. $1{,}875 \pm 188$ ng/mL) of dapsone in combination treatment compared to dapsone alone, respectively. Based on in vitro experiments, the fact that dapsone is primarily catalyzed by CYP2C9 and CYP3A4 (Li et al. 2003) and that pyrimethamine is known to have weak or no inhibition effects on these isoenzymes (Bapiro et al. 2001) makes an interaction at the enzymatic level unlikely. The authors proposed that protein binding displacement may have been the mechanism explaining the increased Vd/F and decreased Cmax, since there was also evidence of increased salivary dapsone concentration (an indirect measure of free plasma drug concentration), suggesting that more free dapsone was available in the presence of pyrimethamine.

Tan-ariya et al. (1998) studied the pharmacokinetic interaction between pyrimethamine (single oral dose of 100 mg) and artemether (single oral dose of 300 mg) in healthy male volunteers of Thai origin ($n = 8$) using an open label, prospective, cross over design. Pyrimethamine did not alter the pharmacokinetics of artemether, as evident by comparable Cmax (511 [301–700] vs. 499 [287–648] ng/mL, median [range]), Tmax (1.8 [1.5–2.5] vs. 2 [1.5–2.5] h), AUC (1.74 [0.97–3.64] vs. 2.16 [0.98–3.67] μg h/mL), t1/2 (2.2 [1.7–3.7] vs. 2.7 [1.8–3.8] h), CL/F (48.5 [24.8–56.6] vs. 37.7 [27.9–75.2] mL/min/kg), and Vd/F (9.1 [6.6–9.4] vs. 9.6 [6.6–11.4] L/kg), when used in combination compared to artemether alone, respectively. Likewise, pyrimethamine had little effect on the pharmacokinetics of the major metabolite of artemether, dihydroartemisinin, as demonstrated by similar Cmax (872 [644–1,570] vs. 885 [654–1,250] ng/mL), Tmax (3.5 [2–5] vs. 2.8 [1.5–4] h), AUC (7.68] 2.4–17.1] vs. 6.5 [2.2–19.2] μg h/mL), and t1/2 (4.9 [2.2–8.2] vs. 5.5 [3.6–8.4] h), when artemether was given concurrently with pyrimethamine compared to artemether alone, respectively. The lack of pharmacokinetic interaction between these two drugs may be supported by the fact that artemether is primarily catalyzed by CYP3A4 (German and Aweeka 2008) in the formation of dihydroartemisinin, but pyrimethamine has no inhibitory effect on this isoenzyme (Bapiro et al. 2001) as shown in in vitro experiments. However, these negative findings should be interpreted in the context of the very small sample size and large variability in all of the pharmacokinetic parameters collected in a setting (i.e. single-dose) not typically applicable to the clinic.

6.12 Effects of Quinidine on the Pharmacokinetics of Antimalarials

The effects of quinidine on the pharmacokinetics of artemether have been described above in the study by van Agtmael et al. (1998).

6.13 Effects of Quinine on the Pharmacokinetics of Antimalarials

The effects of quinine on the pharmacokinetics of primaquine have been described above in the study by Edwards et al. (1993). The effects of quinine on the pharmacokinetics of artemether have been described above in the study by Na-Bangchang et al. (2000). Na-Bangchang et al. (1999) studied the pharmacokinetic interaction between quinine (600 mg orally × 1) and mefloquine (750 mg orally × 1) in healthy male Thai volunteers (n = 7), using a prospective, open label, cross over design. Quinine did not significantly affect the disposition of mefloquine, as evident by comparable Cmax (1,072 [750–1,885] vs. 1,090 [753–1,361] ng/mL, median [range]), Tmax (4 [4–6] vs. 4 [4–6] h), AUC (571 [235–689] vs. 467 [285–583] ng h/mL), CL/F (0.56 [0.36–0.69] vs. 0.47 [0.4–0.89]), t1/2 (17.3 [14.3–33.6] vs. 16.2 [13.6–21.9] h), or Vd/F (17.3 [14.8–23.8] vs. 21.0 [11.8–28.8] L/kg) when given in combination compared to mefloquine, respectively. Because both quinine and mefloquine are metabolized primarily by CYP3A4 (Fontaine et al. 2000; Li et al. 2003), there is a metabolic basis for a potential drug-drug interaction that was not observed in this in vivo study. These negative findings, however, should be weighted in the context of the small sample size and large variability. On the other hand, the combination of quinine and mefloquine resulted in a significant increase in QT_C interval, indicating the presence of a pharmacodynamic interaction.

Lefevre et al. (2002) studied the pharmacokinetic interaction between artemether/lumefantrine (given as consecutive oral doses 80 mg/480 mg over 60 h) and quinine (10 mg/kg iv single dose) in healthy male volunteers, using a prospective, randomized, double-blinded, parallel group design (n = 14/group). Quinine significantly decreased the AUC (35.1 ± 22.2 vs. 63.4 ± 87.5 ng h/mL, mean ± SD), but had little effect on Cmax (23.3 ± 10.0 vs. 30.8 ± 25.4 ng/mL), Tmax (1.92 [1.92–2.3] vs. 1.92 [1.92–3.0], median [range]), and t1/2 (1.6 ± 0.8 vs. 2.3 ± 1.2 h) of artemether when given in combination compared to artemether/lumefantrine given alone, respectively. Likewise, quinine significantly decreased AUC (120 ± 47 vs. 178 ± 71 ng h/mL but had little effect on Cmax (72.3 ± 29.0 vs. 84.5 ± 26.5 ng/mL), Tmax (1.92 [1.92–3.0] vs. 1.92 [1.92–5.0], median [range]), and t1/2 (1.1 ± 0.4 vs. 1.2 ± 0.4 h) of dihydroartemisinin when given in combination compared to artemether/lumefantrine alone, respectively. On the other hand, quinine did not significantly affect the AUC (404 ± 184 vs. 383 ± 304), Cmax (11.4 ± 4.8 vs. 10.0 ± 8.5 ng/mL), Tmax (62 [50–68] vs. 64 [38–66), and t1/2 (164 ± 38 vs. 144 ± 31 h) of lumefantrine in combination compared to the control. The decrease in artemether and dihydroartemisinin exposures in the presence of quinine is difficult to explain in the context of the known metabolic properties of these agents, and may be attributed (as has been noted by the authors) to the large variabilities observed (i.e. chance events) in these data. Overall, these findings are consistent with those reported by Na-Bangchang et al. (2000) which also demonstrated a general lack of drug interaction between quinine and artemether/

lumefantrine despite these agents sharing common metabolic (i.e. CYP3A4) pathways.

6.14 Effects of Sulfadoxine/Pyrimethamine on the Pharmacokinetics of Antimalarials

The effects of sulfadoxine/pyrimethamine on the pharmacokinetics of mefloquine has been described above in the study by Karbwang et al. (1990). Furthermore, Karbwang et al. (1987) studied the effects of combination sulfadoxine/pyrimethamine (single oral dose of 1.5 g/75 mg) on the pharmacokinetics of mefloquine (single oral dose of 750 mg) in healthy female (n = 12) and male (n = 12) Thai volunteers using a prospective, open label, cross over design. In female volunteers, sulfadoxine/pyrimethamine decreased the Tmax (8.7 ± 3.9 vs. 18 ± 6.6 h, mean ± SD) of mefloquine, but had little effect on other pharmacokinetic parameters as evident by comparable Cmax (1,141 ± 420 vs. 1,453 ± 519 ng/mL), t1/2 (22.3 ± 4.1 vs. 17.2 ± 1.9 days), AUC (26.0 ± 9.4 vs. 21.6 ± 6.2 μg day/mL), and Vd/F (19.7 ± 4.1 vs. 17.9 ± 8.2 L/kg) when given in combination compared to mefloquine alone, respectively. In male volunteers, sulfadoxine/pyrimethamine did not affect any pharmacokinetic parameter of mefloquine, as evident by similar Tmax (19 ± 7.0 vs. 23 ± 14 h), Cmax (1,057 ± 145 vs. 1,442 ± 774 ng/mL), t1/2 (19.1 ± 4.4 vs. 15.4 ± 0.9 days), AUC (18.8 ± 4.1 vs. 17.3 ± 6.4 μg day/mL), and Vd/F (20.7 ± 7.3 vs. 19.5 ± 6.1 L/kg) when given in combination compared to mefloquine alone, respectively. When the authors pooled data from all subjects together (i.e. n = 24), only a slightly longer t1/2 (20.7 ± 4.3 vs. 16.3 ± 1.7 days) was observed in the combination group compared to mefloquine alone. These data suggesting minimal effects of sulfadoxine/pyrimethamine on the disposition of mefloquine can be supported by the lack of a known metabolic basis for interactions between these drugs. However, the small sample size accompanied by large variability means the negative finding should be viewed with caution. The pharmacokinetic interaction also remains to be determined in the patient population under steady-state dosing conditions.

Obua et al. (2006) examined the pharmacokinetic interaction between chloroquine (as a single 600 mg oral dose) and sulfadoxine/pyrimethamine (as a single 1,500/75 mg oral dose) in healthy volunteers via an open label, prospective, randomized, parallel group design (n = 8). Sulfadoxine/pyrimethamine did not change the pharmacokinetics of chloroquine in plasma, as evident by comparable Cmax (731 [449–1,194] vs. 760 [466–1,186] mol/L, median [range]), AUC_{last} (43 [26–70] vs. 34 [19–54] mmol h/L), Tmax (3 [1–3] vs. 2 [1–4] h), t1/2 (162 [102–395] vs. 155 [85–232] h), Vd/F (105 [79–203] vs. 113 [55–257] L/kg), Cl/F (0.44 [0.28–0.72] vs. 0.50 [0.39–0.77] mL/h/kg), and bioavailability (1.26 [1.03–1.36] vs. 1), for the combination compared to chloroquine alone, respectively. The small sample size and the very large variability should be taken into

context of these negative findings, although the lack of significant pharmacokinetic interaction is supported by the known metabolic properties of these agents that do not support an interaction at the CYP450 enzymatic level.

6.15 Effects of Tafenoquine on the Pharmacokinetics of Antimalarials

Miller et al. (2013) examined the pharmacokinetic interaction between tafenoquine (900 mg orally daily × 2) and chloroquine (600 mg orally daily × 2, then 300 mg × 1) in healthy volunteers (n = 20), using a prospective, randomized, double blind design. Tafenoquine did not affect the pharmacokinetics of chloroquine, as evident by the similar geometric mean ratios of AUC_{∞} (1.00 [0.84–1.18], mean [90 % CI]), Cmax (1.04 [0.86–1.25]), and t1/2 (0.94 [0.78–1.12]). Likewise, tafenoquine did not change the pharmacokinetics of the major metabolite of chloroquine, desethylchloroquine, as demonstrated by comparable geometric mean ratios of AUC_{∞} (1.19 [0.79–1.79], mean [90 % CI]), Cmax (0.92 [0.72–1.17]), and t1/2 (1.20 [0.79–1.82]). No other pharmacokinetic parameters were reported. The lack of pharmacokinetic interaction translated into a lack of pharmacodynamic interaction between these agents, including a negligible effect on QT prolongation. Because chloroquine is primarily metabolized by CYP2D6, CYP3A4, and CYPC9 (Kim et al. 2003; Projean et al. 2003) and tafenoquine is not known to inhibit these isoenzymes, these negative findings support the lack of metabolism-based interaction between these two agents in a well-powered study.

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Chapter 7
Pharmacodynamic Interactions: Clinical Evidence for Combination Therapy, In Vitro Interactions, and In Vivo Interactions

This chapter summarizes the clinical evidence supporting antimalarial combination therapy and provides details of studies that describe in vivo and in vitro drug interactions in which co-administered antimalarial or non-antimalarial drugs affect the pharmacokinetics of various antimalarials and vice versa.

7.1 Summary of Clinical Evidence for Combination Therapy

Over the last few decades, significant amounts of literature have been published regarding combination therapy for treating malaria. Combination therapy is used to enhance efficacy and decrease resistance to single-agent therapy. In particular, the advent of artemisinin-based regimens has greatly improved treatment outcomes for malaria worldwide. As mentioned in Chap. 1, the currently recommended combination therapies for malaria are artemether-lumefantrine, artesunate-amodiaquine, artesunate-mefloquine, artesunate-sulfadoxine-pyrimethamine (WHO 2010). Additionally, dihydroartemisinin-piperaquine is a promising newly established combination.

From a pharmacodynamics perspective, the combinations have been shown to be effective for malaria treatment. Most studies have been completed with *P. falciparum* but some also exist for *P. vivax*. As giving single-agent treatment is now unethical, most studies compare combination treatment regimens to each other, in order to assess efficacy. Therefore, it is difficult to assess interactions between agents at this level. However, a recent Cochrane review provides an overview of efficacy data and the results of this review are summarized below (Sinclair et al. 2009).

The Cochrane review identified 50 studies that assessed ACTs head to head in uncomplicated *P. falciparum* (Sinclair et al. 2009). Overall, all five regimens

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achieved failure rates of less than 10 %. It was noted that dihydroartemisinin-piperaquine performed well compared to other agents (significantly better than artesunate-mefloquine and artemether-lumefantrine). This may be due in part to less established resistance to this newly available ACT. It was also noted that amodiaquine plus sulfadoxine-pyrimethamine was inferior to ACTs, suggesting the importance of artemisinin-based therapy. Major conclusions from the review are that ACTs still remain first line in malaria management. However, there needs to be continual surveillance throughout endemic regions to ensure therapy maintains efficacy and resistance does not counteract therapeutic success.

7.2 Pharmacodynamic Drug–Drug Interactions In Vitro

Table 7.1 summarizes the known in vitro interactions between recommended antimalarials and other agents.

Early pharmacodynamic studies were important for the advent of ACTs to treat malaria. Gupta et al. (2002a) assessed in vitro interactions of artemisinin with atovaquone, quinine, and mefloquine against *P. falciparum*. Findings were important, as synergism was shown with quinine and mefloquine, while additive activity to synergism was demonstrated with the atovaquone combination. The authors discussed how potential synergism may be questioned due to the rapid action and half-life of artemisinin but hypothesized that with appropriate timing the synergistic effects can be maximized. These findings, along with the others reported below, laid the foundation for the antimalarial combinations we see today.

Knauer et al. (2008) assessed in vitro interactions of quinine compared with retinol. Parasite isolates of *P. falciparum* were taken from patients with malaria contracted in Myanmar or Thailand. Thirty-eight isolates were successfully tested. Retinol significantly enhanced the activity of quinine; EC_{90} (concentration that leads to 90 % of maximal response) values with quinine-retinol were 829 nM, 738 nM, and 762 nM for low, medium, and high concentrations, respectively. This was also reflected by strong reductions in the geometric mean concentration for full inhibition (GMCOC) to 1,990, 1,462, 1,344 nM, respectively; all were deemed to be clinically achievable levels. Results from this study demonstrate that retinol is a potential candidate for future antimalarial combinations and should be assessed in animal and human studies.

Skinner-Adams and Davis (1999) assessed quinine, chloroquine, and artemisinin drugs for in vitro activity with omeprazole. Omeprazole was previously identified as a potential antimalarial agent. Combinations of quinine with omeprazole were found to be synergistic (interaction factor $= 0.622$, $p < 0.001$). However, omeprazole and chloroquine were antagonistic (interaction factor $= -0.730$, $p < 0.001$). Omeprazole combined with artemisinin drugs (artemisinin, dihydroartemisinin, artesunate, artemether) was found to exhibit additive interactions only. An antagonistic interaction was also found between quinine and chloroquine (interaction factor $= -2.836$, $p = 0.005$). The authors concluded that omeprazole could be a

Table 7.1 Summary of in vitro pharmacodynamic drug interactions

Drug or drug class	Antagonism	Additive	Synergism	None or inconclusive
Artemisinins • Artemisinin • Artemether • Artesunate • DHA	Cepharanthine Choloroquine Ketoconazole	Amphothericin B Azithromycin Chloroquine Clindamycin Clotrimazole Methylene Blue Omeprazole	Amodiaquine Atovaquone Chalcones Clindamycin DBB DEAQ Doxycycline Mefloquine Methylene Blue Pyronaridine Quinine Retinol + Mefloquine Triclosan	Atorvastatin N-Acetylcysteine Pyronaridine (Artesunate) Piperaquine (DHA) Rosuvastatin
Amodiaquine and DEAQ	Chloroquine Methylene Blue		Artemisinins Atorvastatin Quinine Retinol	
Atovaquone	Chloroquine Mefloquine Methylene Blue Quinine	Cepharanthine	Amodiaquine Artemisinins Cepharanthine DEAQ Proguanil Retinol Tetracycline	
Chloroquine	Amodiaquine Artemisinins Atorvastatin Mefloquine Methylene Blue Omeprazole Quinine Suladoxine-Pyrimethamine	Artemisnins Azithromycin Cepharanthine DECQ Methylene Blue	Azithromycin Cepharanthine Retinol	Piperaquine
Lumefantrine		Cepharanthine	Cepharanthine DBB	
Mefloquine	Atorvastatin Cepharanthine Chloroquine	Methylene Blue	Artemisinins Methylene Blue Retinol	Piperaquine
Piperaquine		Cepharanthine	Cepharanthine	Quinine Chloroquine DHA Mefloquine
Primaquine		Azithromycin	Azithromycin	

(continued)

Table 7.1 (continued)

Drug or drug class	Antagonism	Additive	Synergism	None or inconclusive
Proguanil			Atovaquone DBB	
Quinidine/ Quinine	Atorvastatin Chloroquine	Azithromycin Methylene Blue	Amodiaquine Artemisinins Azithromycin DEAQ Omeprazole Methylene Blue Retinol	Piperaquine
Sulfadoxine-Pyrimethamine	Chloroquine Methylene Blue			

DBB desbutyl-benflumetol, *DEAQ* desethylamodiaquine, *DECQ* desethylchloroquine, *DHA* dihydroartemisinin

potential antimalarial agent. However, due to the limited activity and widespread use of proton-pump inhibitors, this is unlikely to occur.

Kerschbaumer et al. (2010) assessed mefloquine and artemisinin, in addition to enhancement with retinol. Forty-three *P. falciparum* isolates were taken from patients in Thailand. These isolates were tested for response to retinol alone, mefloquine alone, artemisinin alone, mefloquine-artemisinin 5:1, and mefloquine-artemisinin 5:1 with fixed concentrations of retinol corresponding to the 50th, 65th, and 80th percentile of the mean concentrations found in blood of healthy adults. Full inhibition of parasite maturation was found at concentrations of 38,205.5 nM (mefloquine) and 2,765.8 nM (artemisinin); and for the combination, concentrations were 11,124.0 nM (mefloquine) and 111.2 nM (artemisinin). Retinol further enhanced this synergistic finding (concentrations of 5,412 nM [mefloquine] and 54.2 nM [artemisinin] for low; 4,136.0 nM [mefloquine] and 41.4 nM [artemisinin] for medium; and 3638.0 nM [mefloquine] and 3.4 nM [artemisinin] for high). Again, retinol appeared to be a potential agent to be used in combination for treatment of malaria.

Gruber et al. (2009) evaluated the interaction between mefloquine and retinol after observing synergism with quinine. Thirty-seven isolates of *P. falciparum* were obtained from Thai patients. Concentrations of retinol at the 50th, 65th, and 80th percentiles of physiological levels were studied. The mean IC50, IC90, and IC99 (inhibitory concentrations at 50, 90, and 99 %) values for mefloquine were 1.76, 9.81 and 39.78 μM, respectively, for mefloquine alone; 0.33, 1.37, 4.33 μM for low retinol concentrations; 0.29, 1.15, and 3.48 μM for medium concentrations; and 0.20, 0.85, and 2.70 μM for high concentrations. The versatility of retinol makes it a leading candidate for new antimalarial combinations.

Ley et al. (2008) assessed synergy with chloroquine or amodiaquine and retinol. Twenty-nine isolates of *P. falciparum* were obtained from patients in Thailand. Synergism was found with chloroquine; however, this combination is clinically

irrelevant due to resistance patterns of *P. falciparum* to chloroquine. Synergy was also demonstrated with amodiaquine. The GMCOC decreased from 2,520 nM with amodiaquine alone to 1,092, 800, and 745 nM with low, medium, and high concentrations of retinol, respectively. Similar trends were observed with EC50, EC90, and EC99. As above, evidence is growing for the potential use of retinol in combination regimens.

Mariga et al. (2005) evaluated in vitro pharmacodynamic interactions with amodiaquine and its metabolite desethylamodiaquine with artemisinin, quinine, and atovaquone. The three strains of *P. falciparum* originated from Tanzania, Gambia, and Thailand. Synergism (based on EC90) was found between all combinations but most commonly with atovaquone and artemisinin. Some antagonism was found between the other agents but this was mostly strain-specific and synergism was also consistently demonstrated. Findings give promising results that amodiaquine may be combined with agents outside of the artemisinin class, which may be an important consideration for emergence of future resistance patterns to this class.

In vitro atovaquone pharmacodynamic interactions have been described in a number of studies. Canfield et al. (1995) compared multiple antimalarial combinations for potential therapy to enhance efficacy. Findings included antagonistic interactions between atovaquone and the quinolones and artemisinins with synergism established with biguanides and tetracycline. Proguanil emerged as the leading candidate for the combination regimen. A second study by Lutgendorf et al. (2006) compared atovaquone plus proguanil in addition to artemisinin. This study reported synergism between atovaquone and artemisinin alone; but, synergism was more pronounced when proguanil was added. The authors concluded that this triple combination may be considered for a future clinical treatment regimen. In order to further understand the mechanism of interaction between atovaquone and proguanil, a third study by Thapar et al. (2003) evaluated combinations of each. Based on the achieved EC50 and EC90 values, it was determined that the synergism was due to atovaquone and proguanil and may not require the presence of cycloguanil. This is likely due to differences in targets of proguanil and cycloguanil.

Retinol has also been studied with atovaquone in a study by Exner et al. (2007). The EC90 values were lower with the combination therapy at low, medium, and high concentrations. Additionally, the GMCOCs were also lower ($p < 0.05$). Therefore, the authors concluded that retinol may be used to enhance the antimalarial activity of atovaquone, which is in line with previously reported studies that describe synergistic interactions of retinol with antimalarial agents.

Stahel et al. (1988) evaluated chloroquine and its active metabolite desethylchloroquine with the antimalarial drugs, quinine, amodiaquine, mefloquine, pyrimethamine-sulfadoxine, and artemisinin. Findings showed an additive interaction between chloroquine and desethylchloroquine but antagonistic interactions with all the other combinations. The authors concluded that decreased therapeutic efficacy may be a consequence of chloroquine being administered with or around doses of other antimalarials. For these reasons, as well as chloroquine resistance

worldwide, it is not recommended as part of first-line combinations for *P. falciparum*.

Kyavar et al. (2006) assessed chloroquine with artemisinin and desbutyl-benflumetol (DBB) for *P. vivax*. Although not a typical combination, interaction studies found an additive interaction when chloroquine was combined with artemisinin at EC50, EC90, and EC99 values. The DBB combination with artemisinin revealed a significant activity correlation at EC50, EC90, and EC99, demonstrating both additive and synergistic (EC99) interactions. The authors concluded that this combination may be a potential therapeutic alternative for falciparum and vivax malaria. Further studies are needed to confirm in vivo.

Pereira et al. (2011) assessed azithromycin, purported to have antimalarial properties, in combination with chloroquine for chloroquine-sensitive *P. falciparum* in patients in Malawi. Results showed mostly additive interactions for in vitro samples at 96 h. However, at EC90 values, synergy was apparent. The authors also tested the combination in addition to amlodipine in an in vivo mouse model and found 99.9 % of parasitemia suppressed. Amlodipine is known to have resistance reversal properties when used in combination with chloroquine. However, pharmacokinetic/pharmacodynamic modeling suggested that a dose of 1.8 g of amlodipine would be needed to achieve similar efficacy in humans and this would likely not be achieved due to its adverse effect profile. Although azithromycin shows promise, studies are needed to determine true efficacy and resistance profile of this agent.

Bwijo et al. (1997) evaluated the combination of artemisinin and mefloquine in vitro. Chloroquine-sensitive strains of *P. falciparum* were used under repetitive dosing to mimic in vivo conditions. The period of drug dosing was 3 days. Findings showed EC50, 90, and 99 values were significantly lower for both artemisinin and mefloquine when used in combination and produced synergy at concentrations normally reached in vivo ($p = 0.016$). The findings of this study helped support the development of mefloquine as a component in combination therapy.

Arreesrisom et al. (2007) assessed the effect of N-acetylcysteine (NAC) on the anti-*P. falciparum* activity of artesunate. NAC may have antimalarial properties and be a candidate for adjunctive treatment. Interestingly, inhibition of the antimalarial activity of artesunate was observed during the first 6 h and when NAC was pre-incubated with *P. falciparum*. However, no inhibition was noted when NAC was added 2 h after parasite exposure to artesunate. Although positive, this combination is unlikely to add value for malaria treatment.

Piperaquine is a newer antimalarial agent currently recommended in combination with dihydroartemisinin. Davis et al. (2006) aimed to assess in vitro interactions with piperaquine, pyronaridine, naphthoquine with DHA, quinine, mefloquine, and chloroquine. Results found no interaction or only mild antagonism with all combinations. Findings suggested that the clinical significance of any observed antagonism is unknown but likely to be minimal.

Two studies assessed the antimalarial activity of methylene blue in combination with other agents. Methylene blue was formerly used as an antimalarial but research is being conducted to determine its appropriateness for future combination

regimens. Garavito et al. (2007) assessed the activity of methylene blue for *P. falciparum* in combination with amodiaquine, artemether, atovaquone, chloroquine, doxycycline, mefloquine, primaquine, pyrimethamine, and quinine. Findings showed antagonism with amodiaquine, atovaquone, doxycycline, and pyrimethamine; additive behavior with artemether, chloroquine, mefloquine, and primaquine; and synergy with quinine.

Dormoi et al. (2012) assessed methylene blue in combination with chloroquine, monodesethylamodiaquine, quinine, mefloquine, dihydroartemisinin, and atorvastatin for *P. falciparum*. Findings showed antagonism with chloroquine, additive effects with monodesethylamodiaquine, and synergistic effects with mefloquine and quinine. High synergism was noted with dihydroartemisinin and atorvastatin. These findings suggest that methylene blue could become a new target agent for future antimalarial combination regimens.

Ohrt et al. (2002) assessed in vitro outcomes of azithromycin in combination with multiple agents against *P. falciparum*. Studies with chloroquine demonstrated additive and synergistic interactions while quinine, tafenoquine, and primaquine were additive to synergistic. Dihydroartemisinin was additive but trended toward antagonism. Findings suggest that chloroquine-azithromycin may be considered for prophylaxis, while quinine-azithromycin has the potential for malaria treatment. Noedl et al. (2007) assessed azithromycin in combination with dihydroartemisinin or quinine. Findings showed azithromycin to have significant antimalarial activity and when combined with either agent, demonstrated additive (trending toward synergistic) interactions. Again, more research is needed with this agent, especially to consider potential for resistance.

Studies have assessed the interaction between artemisinin and monodebutyl-benflumetol. Muller et al. (2008) assessed this combination in a 1:1 M/M ratio. Interaction studies showed moderate synergism at EC50 and strong synergism at EC90 and EC99. The positive interaction was most pronounced in isolates with reduced sensitivity against artemisinin and monodebutyl-benflumetol. Another study by Raffelsberger et al. (2008) assessed the combination with *P. falciparum* in a 1:3 M/M ratio. Synergism was found between these two agents but became less evident after subsequent analysis. This study also assessed monodebutyl-benflumetol and proguanil in combination. Moderate synergism was found that may be beneficial for future therapeutic use. Findings from these studies warrant in vivo analysis to assess the efficacy and safety of these agents in combination.

Clindamycin has been purported to have antimalarial properties. Ramharter et al. (2003) assessed the combination of clindamycin with dihydroartemisinin in *P. falciparum* isolates. Interaction studies showed additive or synergistic interactions at various concentration ratios (e.g. EC50). No antagonism was identified. A fixed combination showed additive activity at EC90 values and the authors concluded that this combination may be a potential candidate for clinical use. Clindamycin is now recommended as part of second-line combinations for some indications (Sect. 7.1).

Vivas et al. (2008) evaluated the efficacy of pyronaridine and artesunate. In vitro studies showed slight antagonism with *P. falciparum* but this was deemed to be

negligible. In vivo studies of *P. berghei* found increased activity when the agents were used in combination, suggesting additive or synergistic interactions. This combination should be further explored in clinical settings.

As statin agents have been purported to have antimalarial activity, Wong and Davis (2009) assessed atorvastatin and rosuvastatin in combination with chloroquine and dihydroartemisinin. Results showed no beneficial interactions and authors deemed any antimalarial activity present was not sufficient to warrant further study of these drugs as potential therapeutic agents. Based on these findings, it is unlikely that statins will be further assessed as antimalarials.

Cepharanthine is an alkaloid isolated from the plant *Stephania rotunda*. Desgrouas et al. (2014) completed interaction studies to assess the potential of this agent as a component of an antimalarial combination. In vitro testing showed enhanced efficacy with chloroquine, lumefantrine, atovaquone, piperaquine, and monodesethylamodiaquine. However, antagonism was demonstrated with dihydroqrtemisinin and mefloquine. In vivo results showed improved survival of mice when cepharanthine was used in combination with chloroquine or amodiaquine. These findings warrant future study with this agent as part of antimalarial combination therapy.

Leeb et al. (2010) assessed the interaction between lumefantrine and monodesbutyl-benflumetol in 44 isolates of *P. falciparum*. Geometric mean values for complete inhibition of schizont maturation were 1036 nM for lumefantrine, 655 nM for monodesbutyl-benflumetol and 223 nM for the combination. Moderate synergism was found at the IC50 and increased to the highest level at IC99. The authors concluded that this combination may be suitable for future use pending results from clinical trials. This is consistent with other studies that also assessed the utility of desbutyl-benflumetol (Kyavar et al. 2006).

Starzengruber et al. (2008) assessed the same agents in 35 isolates of *P. falciparum*. Results were very similar giving GMCOC values of 537 nM for lumefantrine, 246 nM for monodesbutyl-benflumetol, 236 nM for lumefantrine-monodesbutyl-benflumetol 999:1, and 155 nM for lumefantrine-monodesbutyl-benflumetol 995:5. For the 995:5 combination, synergism was found and increased with effective inhibitory concentrations. These findings further support the development of this drug as an antimalarial combination agent.

Tripathi et al. (2013) attempted to use pharmacokinetic principles to identify a new combination option. Ketoconazole, a potent CYP3A4 inhibitor, was combined with a/B arteether in vitro against *P. falciparum*. Findings showed an additive interaction. The study was taken further with an in vivo analysis using mice and multidrug-resistant *P. yoelii nigeriensis*. Results showed that sub-curative doses of ketoconazole combined with a/B arteether achieved 100 % curative action. While the exact mechanism of action is unknown, the authors speculated that the pharmacokinetic properties of ketoconazole may contribute to these findings.

Ketoconazole was also assessed by Mishra et al. (2007) with artemisinin. Interactions between artemisinin and ketoconazole as well as triclosan were evaluated in cultures of *P. falciparum*. Ketoconazole was found to be antagonistic in vitro. However, triclosan showed mild synergism. The authors stated that no

firm conclusions can be made regarding ketoconazole until the combination is tested in vivo. Although there were discrepant findings between this study and those of Tripathi et al. (2013), further testing can be justified to develop ketoconazole as a potential antimalarial combination agent.

Sponer et al. (2002) assessed the pharmacodynamic interactions between doxycycline, a known antimalarial agent, and artemisinin against 31 fresh isolates of *P. falciparum*. Findings suggested a synergistic interaction at each of the EC50, EC90, and EC99 values. The authors acknowledged that clinical trials with these agents have yielded inconclusive results but their findings suggest a potential therapeutic benefit of this combination. Doxycycline is currently recommended as a prophylaxis agent but not as first-line for treatment.

Bhattacharya et al. (2008) evaluated the pharmacodynamic interaction between amphotericin B or clotrimazole with artemisinin against *P. falciparum* in vitro. Findings showed additive interactions for both agents. These interactions occurred at therapeutically safe concentrations. These agents were also active at different stages of the lifecycle as compared to artemisinin. Authors hypothesized that by aiming for different molecular targets, therapeutic efficacy may be enhanced without development of resistance. This information is useful for development of these agents as well as other drug combinations.

The same authors (Bhattacharya et al. 2009) studied the pharmacodynamics of chalcone derivatives in combination with artemisinin against *P. falciparum* in vitro. Chalcones are aromatic ketones and form a group of natural compounds that are easy to synthesize. Licochalcone A was previously reported to have antimalarial activity. When assessed in combination with artemisinin, these derivatives showed synergistic or additive interactions. Thus, this group of compounds may have potential for future drug development against malaria.

Gupta et al. (2002b) studied a synergistic pharmacodynamic interaction between artemisinin and amodiaquine. Combinations of artemisinin with amodiaquine, pyronaridine, and chloroquine were tested in three strains (2 chloroquine-sensitive, one chloroquine-resistant) of *P. falciparum*. Findings showed synergism between artemisinin, amodiaquine and pyronaridine. However, chloroquine showed only additive properties. The authors concluded that amodiaquine may be suitable for combination therapy with artemisinin. Artesunate-amodiaquine is now recommended as a first-line combination.

7.3 Pharmacodynamic Drug–Drug Interactions In Vivo

Table 7.2 summarizes studies assessing drug–drug interactions in humans and important findings are given below.

De Vries et al. (2000) completed a randomized controlled trial to assess three different antimalarial regimens including quinine alone or in combination with artemisinin. The study used an open label design to assess 7 days of quinine alone (10 mg/kg) vs. a single dose of artemisinin (20 mg/kg) and 3 days of quinine

Table 7.2 Summary of in vivo interactions reported in humans

Reference	Study design/population	Study groups and dosing	Efficacy	Safety	Key findings
Bailey et al. (1993)	PC, DB, double-dummy, N = 12 healthy males	Each period subjects received 3 days of placebo (group 1), nifedipine prolonged action orally 20 mg twice daily (group 2), or felodipine 10 mg orally once daily (group 3). Day 4, subjects received pre-treatment regimen plus quinidine 400 mg orally once. Interval between each study period was 2 weeks	NA	Greater ADRs with felodipine, including headache and lightheadedness. Quinidine prolonged QTc in dose-dependent manner in group 1 but QTc similar during each treatment period	No major clinically significant adverse effects were noted
Bindschedler et al. (2000)	R, DB, PC, N = 42 healthy male volunteers randomized to receive combination mefloquine and AR-LM or either drug alone	Mefloquine × 3 doses (500, 250, 250 mg over 12 h) followed by six doses of AR-LM (80–480 mg over 60 h) or either drug alone	NA	No differences were observed on QTc interval between the three groups	Combination unlikely to result in undesired cardiac effects
Bowles et al. (1993)	R, cross over, 2-week washout period, N = 10 healthy volunteers	Quinidine sulfate 200 mg orally, nifedipine 20 mg orally, or combination of both every 8 h for 4 doses (2-week washout between treatments)	NA	Combination had increased heart rate at 0.5, 1.0, 1.5 h compared to 0 h ($p < 0.05$). Maximum change occurred at 0.5 h (17.9 beats/min) and correlated with nifedipine serum concentrations ($r = 0.78$). No effect was observed on mean arterial pressure	Quinidine enhances nifedipine pharmacologic response

de Vries et al. (2000)	R, OL, controlled N = 268 patients aged 8 to 65	Quinine (10 mg/kg) monotherapy × 7 days; artemisinin (20 mg/kg) (1 dose) followed by quinine × 3 days; artemisinin (1 dose) followed by quinine × 5 days	Recrudescence higher in 3 days group vs. quinine and 5 days group (38 vs. 16 vs. 15 %, respectively), $p < 0.001$	NR	Artemisinin-quinine a potential option for malaria treatment
German et al. (2007)	Drug interaction study, N = 5 healthy volunteers	AQ/AS alone (days 1–3), then AQ/AS (days 18–20) combined with efavirenz (days 7–23)	NR	N = 2 developed increases in transaminases 34 and 42 days after study completion N = 1 withdrew after day 3 due to nausea N = 2 removed from study prior to receiving second course of AQ/AS	Study discontinued prematurely. Patient 1 had ALT of 206 U/L and AST of 78 U/L. Patient 2 had ALT of 868 U/L and AST of 559 U/L
Hidalgo et al. (2011)	Case report, N = 1 (53 years old African American male with HIV)	Warfarin 5 mg/day for 12 months after diagnosis of deep vein thrombosis and pulmonary embolism and atovaquone 1,500 mg daily for PCP prophylaxis (both initiated at same time)		7 days after starting both agents, INR was 3.5 and remained high throughout the following 6-week period despite dosage modifications. Atovaquone was discontinued and INR normalized	A pharmacodynamic interaction may exist between atovaquone and warfarin
Hung et al. (2004)	R, PC, N = 360 patients ≥6 years old with 28 days follow up	Artesunate 4 mg/kg given to all patients, then mefloquine 15 mg/kg simultaneously (A), 8 h later (B), 24 h later (C). Mefloquine placebo given to complete regimens	Parasites reappeared in 26 (A), 26 (B), and 33 % (C)	Adverse effects equally distributed over three groups	All mefloquine concentrations achieved target ranges. No interaction between these two agents was observed for efficacy, tolerance, pharmacokinetics

(continued)

Table 7.2 (continued)

Reference	Study design/population	Study groups and dosing	Efficacy	Safety	Key findings
Kaukonen et al. (1997)	R, DB, 2-phase, cross-over, N = 9 healthy volunteers	Itraconazole 200 mg orally daily × 4 days or placebo. A single oral dose of quinidine sulfate 100 mg was given on day 4	NA	QTc interval prolonged during both phases but greater in itraconazole phase ($p < 0.05$). QTc interval correlated with quinidine concentrations during both itraconazole and placebo phases ($r^2 = 0.71, 0.79$; $p < 0.001$). NS changes observed for PQ, QRS, heart rate, or blood pressure	Caution to be taken when quinidine administered with interacting agents
Kusuhara et al. (2011)	Single-arm, four-phase study with N = 8 healthy male subjects (7 days washout between phases)	Phase 1: Metformin 100 mg orally once Phase 2: Metformin 100 mg orally once with pyrimethamine 50 mg orally 1 h before metformin Phase 3: Metformin 250 mg orally once Phase 4: Metformin 250 mg orally once with pyrimethamine 50 mg orally 1 h before metformin	NA	12 h post metformin 250 mg, plasma lactate lower in those with pyrimethamine (11.5 vs. 9.4 mg/dL, $p < 0.01$) but ratio of lactate to pyruvate did not differ significantly. Transient increase in creatinine occurred after metformin 250 mg but continuous increase only observed in pyrimethamine phase. Renal clearance of creatinine reduced in pyrimethamine phase (145 vs. 116 mL/min, $p < 0.01$) in 250 mg metformin group	A drug–drug interaction may exist between metformin and pyrimethamine

Laganiere et al. (1996)	R, four-period cross over study, N = 12 healthy volunteers	Single oral dose of quinidine 200 mg with and without oral diltiazem SR 90 mg twice daily for five doses with last dose given 90 min before quinidine. Also, single oral dose diltiazem SR 60 mg with and without oral quinidine pre-treatment 100 mg twice daily for 5 doses with last dose given 90 min before diltiazem	NA	Diltiazem pre-treatment increased QTc, PR intervals and decreased heart rate and diastolic blood pressure but were not significant once corrected for baseline. No differences found with quinidine pre-treatment	No major pharmacodynamic interaction found
Miller et al. (2013)	R, DB, parallel group, N = 58 healthy adults aged 18–55 years	CQ 600 mg days 1–2, 300 mg day 3 (N = 20) TQ 450 mg days 2–3 (N = 20) CQ + TQ (as above dosing) (N = 18) All medication given orally in the AM	NA	Increased QTc interval in CQ group but not TQ group. CQ + TQ group was similar to CQ group. No subject had QTc > 48 ms or change from baseline of ≥60 ms	No clinically significant interactions were observed
Na-Bangchang et al. (2000)	R, 7-way crossover trial, N = 8 healthy male volunteers	AR 300 mg × 1 dose MQ 650 mg × 1 dose QN 600 mg × 1 dose PQ 45 mg × 1 dose AR + MQ AR + QN AR + PQ	NA	No ADRs reported after AR, QN, PQ alone or in combination. MQ (alone or in combination) produced weakness, nausea, abdominal pain, and diarrhea in 3 patients and 1 patient had dizziness	Combination regimens with AR may be safe and well tolerated

(continued)

Table 7.2 (continued)

Reference	Study design/population	Study groups and dosing	Efficacy	Safety	Key findings
Omoruyi et al. (2007)	R, Latin square, pharmacokinetic cross over study (8-week washout period), N = 10 healthy male volunteers	Halofantrine 500 mg orally × 1 dose alone or with 600 mg AQ given 24 h before halofantrine	NA	Non-significant increase in QTc interval with combination regimen	AQ and halofantrine may pose cardiac risk when administered together
Sinou et al. (2009)	Uncontrolled study, N = 13 adult patients with *P. falciparum* parasitemia of at least 2,000 parasites per mcL and temperature >37.5 °C or history of fever in preceding 24–48 h	AQ-AS (600–200 mg) orally daily × 3 days	All patients afebrile on day 3, parasitemia cleared by day 2. N = 1 recurrence within 28 days follow up period	NR	AQ-AS may be effective for highly drug resistant *P. falciparum* malaria
Supanaranond et al. (1997)	Uncontrolled study with N = 13 adults with uncomplicated *P. falciparum* malaria	Oral mefloquine hydrochloride (15 mg/kg base) given with 1 h i.v. infusion of quinidine hydrochloride (10 mg salt/kg)	All patients recovered without complications	QTc interval longer post-treatment than pre-treatment (0.44 vs. 0.40s, $p < 0.05$). NS difference for heart rate, blood pressure, PR interval	No evidence of major cardiovascular interaction between these two agents
Turgeon et al. (1990)	OL, 4-phase study with N = 8 extensive metabolizer encainide and N = 2 poor metabolizer encainide with high frequency, temporally stable, non-sustained ventricular arrhythmias	Phase I: No therapy Phase 2: Encainide 25 mg orally every 12 h Phase 3: Encainide 25 mg orally every 12 h and quinidine sulfate 60 mg every 8 h	Low-dose encainide decreased ventricular ectopic depolarization frequency by 64 ± 22 % from baseline ($p < 0.05$) and combination with quinidine suppressed 77 ± 19 % from baseline ($p < 0.05$). The	Non-significant changes observed with QTc throughout study	Genetics may influence potential drug interactions

		Phase 4: Quinidine sulfate 60 mg every 8 h (Each phase lasted at least 4 days)	difference between groups was significant ($p < 0.05$)		
Wang et al. (2014)	R, PC, DB, N = 100 *Toxoplasma gondii* seropositive patients with schizophrenia (antipsychotic-naïve)	All patients started on risperidone 0.5 mg orally twice daily and titrated every other day based on clinical presentation within first 3 weeks. Group 1 received AR 80 mg daily during second week (days 8–14) and fourth week (days 22–28). Group 2 received placebo	AR group greater reduction in PANSS negative symptom scale ($p = 0.03$) and Clinical Global Impressions Scale ($p = 0.01$) but non-significant in PANSS positive symptom and general psychopathology scales ($p > 0.05$)	Dropout rates and adverse drug reactions similar between groups. 1 patient in AR group dropped out due to nausea/vomiting	AR does not appear to be highly efficacious for cognitive deficits in schizophrenia
Yasuhara et al. (1990)	DB, PC, N = 16 healthy volunteers	Group A (N = 5): Propranolol 10 mg orally × 1 dose with placebo and 7 days later repeated propranolol with 100 mg oral quinidine 12 h before and at the time of propranolol dosing. Group B (N = 11): Same protocol but with 20 mg propranolol and 200 mg quinidine		2 h after each dose of propranolol, increases in heart rate during exercise (treadmill) were significantly suppressed in higher dose trial (-13.8 ± 3.4 vs. -20.1 ± 2.7 bpm; $p < 0.05$). NS difference in blood pressure	Quinidine may enhance propranolol action

ADR adverse drug reaction, *ALT* alanine aminotransferase, *AQ* amodiaquine, *AR* artemether, *AS* artesunate, *AST* aspartate aminotransferase, *bpm* beats per minute, *CQ* chloroquine, *DB* double blind, *INR* international normalized ratio, *IQR* interquartile range, *i.v.* intravenous, *LM* lumefantrine, *MQ* mefloquine, *NA* not available, *NR* not reported, *NS* non-significant, *OL* open label, *PANSS* positive and negative syndrome scale, *PC* placebo controlled, *PQ* primaquine, *QN* quinine, *R* randomized, *SR* sustained release, *TQ* tafenoquine

or a single dose of artemisinin and 5 days of quinine. Clinical failure was defined as no improvement with the need for additional treatment within the first 48 h of therapy (early failure) or after 48 h of therapy (late failure). Results showed higher rates of recrudescence with shorter durations of therapy. Findings suggest that all three regimens may be effective for treating malaria but shortening the duration of quinine reduces success rates. Currently recommended durations of therapy involving quinine reflect this finding.

Hung et al. (2004) completed a clinical interaction study in Vietnamese patients infected with *P. falciparum*. The study was primarily designed to establish efficacy of a single-dose regimen for artesunate-mefloquine. Secondary objectives were to study the tolerance, pharmacokinetics, and pharmacodynamics of different timing of the mefloquine dose. The study was randomized, double blinded, and placebo controlled. Group A received a single dose of artesunate (4 mg/kg) and mefloquine (15 mg/kg) at the same time. Group B received the mefloquine dose 8 h after the artesunate dose and Group C received the mefloquine dose 24 h after the artesunate dose. One patient in Group C was classified as early failure after decompensating within 8 h. Three patients had parasites detectable on day 7 but recovered completely and were classified as clinical cure. Three patients left before any endpoint could be measured and two did not return for follow up on day 7. Initial treatment outcome was similar between the three groups, suggesting similar efficacy. Reappearance of parasites appeared in 26, 26, and 33 % of patients (Groups A, B, and C, respectively) also suggesting similar efficacy. Adverse drug reactions were common (dizziness, muscle pain, anorexia, arthralgia, nausea, tremor, dry mouth, and vomiting) but similar between groups. The similarities between efficacy and tolerability rates for each regimen suggest no major pharmacodynamic interaction exists. However, it is unclear if the combination has any effect on decreasing resistance to mefloquine over time.

Sinou et al. (2009) completed an uncontrolled study that assessed daily amodiaquine-artesunate for 3 days. Thirteen patients were enrolled and efficacy was assessed by temperature, signs and symptoms, and parasite clearance. Results showed all patients became afebrile on day 3 and parasitemia cleared by day 2. A rapid reduction in clinical signs and symptoms was also noted. Genotypic analysis showed presence of drug resistant strains. These findings suggest that amodiaquine-artesunate may be a regimen of choice for falciparum malaria and potentially effective for drug resistant *P. falciparum* strains.

German et al. (2007) assessed safety outcomes of amodiaquine-artesunate in addition to efavirenz in 5 healthy volunteers. The study was stopped early due to increases in transaminases found in two patients and withdrawal of another patient due to nausea. The adverse effects occurred after addition of efavirenz (patients received 3 days of amodiaquine-artesunate alone prior to efavirenz). As efavirenz is a commonly used HIV-antiviral in endemic regions of malaria, caution is needed when using these agents in combination.

The QTc interval is an outcome of interest in combination therapy, especially as many antimalarials are known to have adverse cardiac effects. Omoruyi et al. (2007) completed a randomized cross over study to assess the effect of

halofantrine in combination with amodiaquine in 10 healthy Nigerian males. Although no statistically significant difference in QTc was found, a non-significant increase was observed that could put patients at risk of cardiac arrhythmias. The small sample size may have precluded any significant findings. Additionally, QTc interval is a surrogate marker and using it to interpret risk may be difficult.

Bindschedler et al. (2000) completed a randomized controlled trial that assessed mefloquine in combination with artemether-lumefantrine. Forty-two healthy males were evaluated ($n = 14$ mefloquine alone, $n = 14$ artemether-lumefantrine alone, $n = 14$ combination). Findings showed no increase in QTc interval (alone or in combination) and also no effect on heart rate. Therefore, these regimens were deemed to be safe and free from adverse cardiac effects. Future studies should assess efficacy and toxicity of triple combination therapy in diseased patients.

Laganiere et al. (1996) studied the effect of a single oral dose of quinidine in patients receiving diltiazem on day 3 of diltiazem treatment. Interestingly, this combination increased the QTc and PR intervals. Heart rate and diastolic blood pressure also decreased. However, after baseline correction, no significant differences remained for any parameter. Quinidine was further studied in a randomized controlled trial that evaluated its interaction with itraconazole (Kaukonen et al. 1997). QTc interval was significantly prolonged ($p < 0.05$) when this combination was given together. No significant differences were found in other parameters such as PQ and QRS intervals, heart rate, or blood pressure. The findings from these two studies (Laganiere et al. 1996; Kaukonen et al. 1997) signal some safety concerns with quinidine and care should be taken when given in combination with any agent known to have adverse cardiac effects.

Other studies showed variable and mostly inconclusive results with quinidine or quinine. Supanaranond et al. (1997) assessed the combination of mefloquine and quinine on QTc interval. It was found that the QTc was longer post-treatment with quinine compared to pre-treatment, but the difference was only 0.04 s. No other cardiac parameters were affected. Turgeon et al. (1990) found only non-significant QTc changes when low-dose encainide was given with quinidine. Lastly, Bailey et al. (1993) assessed felodipine or nifedipine in combination with quinidine and found dose-dependent QTc prolongation with quinidine, but no major clinically significant adverse effects were noted. These studies are important to highlight potential cardiac toxicity with quinidine/quinine and should be considered when patients are taking cardiac medications in addition to the antimalarials.

Bowles et al. (1993) completed a randomized cross over study assessing the combination of quinidine and nifedipine in 10 healthy volunteers. Results showed increased heart rate (maximum increase noted at 0.5 h) when given in combination and this was correlated with nifedipine serum concentrations. However, no effect was noted on mean arterial pressure. It is likely that the pharmacological effect of nifedipine was enhanced by quinidine. Similarly, Yasuhara et al. (1990) assessed a potential interaction between quinidine and propranolol. Twenty healthy volunteers were enrolled and divided into two groups: propranolol 10 mg and quinidine 100 mg vs. propranolol 20 mg and quinidine 200 mg. Results showed suppression

($p < 0.05$) of heart rate during exercise in higher dose groups. However, no blood pressure effects were noted. Again, these studies signal the importance for diligence when combining quinidine with cardiovascular or cardiotoxic medications.

Na-Bangchang et al. (2000) assessed the safety of artemether with multiple quinoline-based agents. Each of artemether, mefloquine, quinine, or primaquine was given alone and then in combination with artemether. The study was performed as a randomized controlled trial with a 7-way cross over design in healthy males. No adverse effects were reported for artemether, quinine, or primaquine alone or in combination, while mefloquine (both alone and combination) produced weakness, nausea, abdominal pain, and diarrhea in three patients. One patient also reported dizziness. Findings from this study are important to consider when designing combination regimens, as tolerability is a major concern of any combination therapy and these regimens were proven safe.

As discussed, antimalarial interactions are not merely important between agents used to treat malaria but also with agents used for treatment of other conditions. The anticoagulant, warfarin, is prone to many pharmacokinetic and pharmacodynamic interactions. Hidalgo et al. (2011) described a case report of an interaction between warfarin and atovaquone. Atovaquone was being dosed at 1,500 mg daily for *Pneumocystis jiroveci* pneumonia prophylaxis and warfarin was being dosed at 5 mg per day. Seven days after starting both agents, the patient's international normalized ratio (INR) became elevated (3.5) and remained high despite dosage modifications. Once atovaquone was discontinued, the INR normalized. Based on this report, it is likely that an interaction exists between these agents and close monitoring of INR and patient signs and symptoms is needed when warfarin is co-administered with atovaquone.

Kusuhara et al. (2011) completed a single-arm study (4-phase cross over) that assessed whether or not there is an interaction between metformin and pyrimethamine. Their findings suggest that an interaction may exist between these two agents. First, plasma lactate was lower when pyrimethamine was combined with metformin ($p < 0.01$). Also, a normal transient increase in serum creatinine upon initiation of metformin was sustained when co-administered with pyrimethamine and renal clearance of pyrimethamine was also reduced. Although clinical significance is unknown for short-term use, patients taking pyrimethamine for prophylaxis may need to be closely monitored if it is given in combination with metformin.

Lastly, Wang et al. (2014) completed a randomized controlled trial that assessed pharmacodynamic interactions between artemether and risperidone in antipsychotic-naïve schizophrenic patients seropositive for *Toxoplasma gondii*. It was previously noted that artemisinin agents may have efficacy for mental health disorders. Patients receiving artemether vs. placebo had greater reductions in the negative symptom scale of the Positive and Negative Symptom Scale (PANSS) and Clinical Global Impressions Scale. However, no difference was found in the PANSS positive symptoms scale or general psychopathology scales. From a safety perspective, dropout rates were similar between groups. These findings show that artemisinin agents are unlikely to have any significant benefit in treating

schizophrenia patients. This is an important consideration as widespread use of these agents may promote the development of resistance to malaria itself.

7.4 Summary

Pharmacodynamic interactions exist between antimalarial agents themselves, or between other agents that may be co-administered for other indications. In vitro studies have assessed synergistic, additive, and antagonistic combinations which have been further developed in in vivo models and eventually clinical trials. It should be noted, however, that any agent demonstrating synergistic antimalarial activity still needs to be adequately assessed to determine potential for resistance as well as clinical-related adverse effects. More research is needed to ensure patients remain safe and therapy remains effective when multiple drugs are administered concurrently. This includes not only agents used synergistically but also when drugs with potential pharmacodynamic interactions are co-administered.

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Chapter 8
Limitations, Future Directions, and Conclusions

We have conducted a systematic qualitative review on the pharmacokinetic and pharmacodynamic drug-drug interactions associated with antimalarial agents recommended by the World Health Organization. In this review, we have identified a few limitations in the available literature. These limitations, as well as suggested future experiments to overcome these shortcomings, are summarized below.

8.1 Limitations and Future Directions Related to Pharmacokinetics

In vitro metabolism studies: Every antimalarial agent discussed in this review has been studied in (an) in vitro system(s) to characterize the primary metabolic enzymes responsible for their biotransformation. While many studies have used the currently accepted industry standards for conducting reaction phenotying studies, a few studies did not attempt the full complement of the various suggested approaches. Specifically, (1) virtually all in vitro studies utilized variants of cDNA-expressed/recombinant enzymes but few employed a full panel of these enzymes; (2) although many studies conducted correlational analyses with known enzyme-specific probe substrates and inhibition experiments using enzyme-selective chemical inhibitors in human liver microsomes, few studies actually used enzyme-"specific" immunoinhibitory antibodies which are required for the definitive assignment of relative contributions; (3) most studies focused on the role of CYP450 isoenzymes whereas the contributions of other metabolic pathways (e.g. phase II, phase III enzymes) remain largely undetermined; (4) all studies used isolated in vitro enzyme systems (such as human liver microsomes) and thus were not able to assess the roles and effects of sequential metabolic processes (e.g. artemether being hydrolyzed via CYP450 enzymes to dihydroartemisinin, which is subsequently conjugated by UGT enzymes, which can potentially affect

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the further biotransformation of its substrate) on the metabolism of substrates/metabolites; and lastly (5) few studies examined the contribution of extra-hepatic (e.g. intestinal) metabolic enzymes that can also contribute to the overall clearance of antimalarial agents. Some of these limitations may have resulted in apparent inconsistencies observed in these in vitro studies. For example, discrepancies in the roles of various CYP450 enzymes responsible for the metabolism of proguanil to cycloguanil were evident between data reported by Birkett et al. (1994), Lu et al. (2000), and Coller et al. (1999).

Some shortcomings of the in vitro systems discussed here for the purpose of pharmacokinetic studies may be overcome with the use of additional/complementary in vitro systems such cDNA-expressed UGT enzymes, microsomal systems with added co-factors suitable for the study of phase II reactions, CaCo2 cell system for the study of drug transporters, or extra-hepatic microsomal systems. However, a unifying approach such as the cultured human hepatocytes, which essentially contains the whole complement of metabolic enzymes in their native conformation (i.e. rather than isolated in vitro microsomal systems), would allow the characterization of the full metabolic process. Ideally, fresh human hepatocytes should be used since cryo-preserved cells may have reduced metabolic activity. However, there are also limitations to this in vitro system, including the scarcity of live-donor human hepatocytes, unknown modulatory effects of culture medium or culture conditions affecting metabolic enzymes, unknown stability of chemical inhibitors/antibodies in the culture medium, or the short longevity of seeded cells, which may all preclude the routine use of this approach. For any drug reaction phenotying study, a full validation of the in vitro hepatocyte culture model is needed prior to conducting pharmacokinetic studies, and the typical academic lab may not have the resources and facilities to carry out these validation activities.

In vivo human studies: A large body of literature has been identified for in vivo human interactions involving antimalarial drugs, and commonly occurring limitations are found in these studies: (1) Each identified study consisted of a relatively small and sometimes convenient sample size ($n < 20$). This is a major limitation because the variabilities in the reported pharmacokinetic parameters in all studies are large (Chaps. 4–6) and many studies have reported (potentially false) negative findings in the absence of a power analysis. (2) The majority of studies employed a single-dose design for either the modulator or effector drug, which deviates from typical dosing guidelines in the clinic. While it may be more costly and complex to design experiments based on steady-state or clinically-relevant multiple-dosing conditions, conclusions derived from single-dose designs may be inconsistent with and in most cases cannot be extrapolated to reflect steady-state conditions. For example, the lack of apparent pharmacokinetic interaction between artemether/lumefantrine and mefloquine observed in the study by Lefevre et al. (2000) is inconsistent with that reported by Na-Bangchang et al. (1995), which may be attributed to differences in study design (e.g. single vs. steady-state). (3) Many

studies consist of only male and/or healthy subjects, potentially limiting the generalizability of the data. The association between gender and pharmacokinetics of antimalarial drugs is well documented [e.g. (Binh et al. 2009)]. Likewise, there are distinct differences in the pharmacology of antimalarial drugs in diseased compared to healthy subjects [e.g. (Teja-Isavadharm et al. 2001)]. However, less is known about the effect of gender/malarial infection on drug-drug interactions, which needs to be considered when extrapolating data obtained only from male healthy subjects. (4) Based on the metabolic characteristics obtained from in vitro experiments, many potentially relevant drug interactions may be predicted yet remain to be tested. Despite the large body of in vivo human studies identified in this review, these still represent only a small fraction of all possible drug interactions that may take place for these reviewed antimalarial drugs. On the other hand, adding another layer of complexity, certainly not all in vivo drug-drug interaction data can be explained by currently known in vitro drug characteristics (see various examples detailed in the text). Only until the complete metabolic profile for a particular drug is obtained using a complete in vitro approach (see limitations for in vitro studies above) can one rely on in vitro data to predict clinically-relevant drug interactions. (5) Most of the studies identified in this review have focused on drug interaction-associated metabolism whereas other pharmacokinetic processes such as absorption, distribution, or elimination, which are all well known to mediate clinically-relevant drug interactions, should also be considered. (6) Finally, the majority of the pharmacokinetic studies do not correlate pharmacokinetic changes to quantitative pharmacodynamic outcomes. This is a major limitation because statistically significant pharmacokinetic changes are only relevant as a surrogate if they can be used to predict efficacy or toxicity outcomes. Future study designs certainly need to have sufficient power to establish the pharmacokinetic-pharmacodynamic relationship rather than focusing just on one or the other.

A technique that can potentially resolve some of the identified shortcomings in these in vivo human studies is population pharmacokinetic-pharmacodynamic modeling (Kiang et al. 2012). Because the technique allows the use of sparse and less-controlled data collection, retrospective analyses can be conducted on already existing clinic data or interaction databases, and prospective experiments using a broader selection of dosing regimens in a heterogeneous patient population can be designed to gather "real clinic" interaction data. To our knowledge, such population modeling data from drug-drug interaction studies are still scarce in the literature.

8.2 Clinical Decision Algorithm: Pharmacokinetics

This book has summarized the in vitro pharmacology and in vivo human interaction data on various antimalarial drugs. In conjunction with this information, the following clinical decision-making algorithm is proposed to assess/predict clinically-relevant drug-drug interactions with antimalarial agents:

1. Does the effector drug possess pharmacokinetic properties (i.e. absorption, distribution, metabolism, elimination) that can be subjected to drug interaction? *As discussed above, most of the studies have focused on metabolism, and these data have been derived from in vitro investigations.*
2. What are the pharmacokinetic properties of the effector drug (i.e. absorption, distribution, metabolism, elimination) that will likely cause a drug interaction? *The same limitations apply here that the majority of the available data focused on drug metabolism and were based on in vitro studies.*
3. Is there evidence that the combination has caused statistically significant changes in drug pharmacokinetics in humans? *The evidence may be appropriately weighted based on limitations in study design (described above). The available human data represent only a small fraction of all the possible drug interactions for these antimalarial agents.*
4. Is there evidence that a significant pharmacokinetic interaction is associated with a pharmacodynamic interaction? *These data are scarce in the literature.*

8.3 Limitations and Future Directions Related to Pharmacodynamics

In vitro studies: Our search identified a number of studies assessing in vitro interactions between agents with antimalarial activity. Research is available in this topic area due to the need for effective combination therapies that decrease the potential for antimalarial resistance. However, a number of limitations were identified that can provide insight for future research in this area: (1) The majority of the studies assessed currently recommended agents and very few studies were identified that assessed agents with future potential (with exception of a few agents such as retinol and methylene blue). Most endemic regions consist of low-income countries and this is likely why there is not a large amount of research available. International organizations should prioritize new combinations of antimalarials and offer compensation for development. (2) Studies that assessed the same agents typically found conflicting results. Often, synergy was found in one study but antagonism or no interaction in another. This creates challenges for researchers to determine which combinations should be further assessed in clinical trials. (3) As many of the studies were reported in the 1990s and early 2000s, results may not be able to be extrapolated to the modern day trends in resistance patterns and multi-drug resistant organisms. Those that reported on resistant strains were not well highlighted and did not commonly separate data from drug sensitive strains. Studies are needed to assess drug resistant strains, especially in the advent of artemisinin resistance.

In vivo human studies: While studies were identified that reported pharmacodynamic outcomes associated with drug combinations, limitations can also be noted.

(1) Very few drug classes were reported that were outside of agents used to treat malaria. With increasing use of chronic disease medications throughout malaria endemic regions, very little evidence is available to help with clinical decision making. (2) Most studies reported only cardiovascular outcomes such as QTc prolongation and bradycardia. While these are important outcomes to assess, very little information exists for other outcomes such as central nervous system toxicity, hepatic and renal function as well as haematological considerations. As use of medications continues to increase worldwide, both clinical and observational studies should be completed to provide guidance for using these agents in combination with other medications. (3) The majority of the studies identified were of relatively low quality, primarily limited by small sample sizes. Small sample sizes increase likelihood of making a type 2 error, where no significant effects are seen even though an effect may exist. Therefore, results from these studies must be interpreted carefully and any patient at risk of pharmacodynamic interactions must be closely monitored even in light of evidence suggesting combinations are 'safe'.

8.4 Clinical Decision Algorithm: Pharmacodynamics

This book has summarized the in vitro and in vivo human studies assessing pharmacodynamic interactions related to both efficacy and safety. In order to provide insight for clinicians considering co-administration of drugs in conjunction with antimalarials, a clinical decision-making algorithm is proposed to assess/predict clinically-relevant interactions:

1. Does the effector drug possess pharmacodynamic properties (effect on drug or effect on body) that may increase likelihood of drug interactions with antimalarials? *Data are limited with respect to drug classes assessed.*
2. Does the potential combination pair have overlapping toxicities that could subject patients to harm (e.g. QTc prolongation, bradycardia, gastrointestinal complaints)? *Most of the studies have focused on cardiovascular-related toxicities (*e.g. *arrhythmias, bradycardia) but clinicians should be aware of any overlap in the complete side effect profiles.*
3. Is there evidence that the combination has caused statistically significant changes in drug pharmacodynamics in humans? *Evidence is limited and must be weighed against study limitations. The available human data represent only a small fraction of all the possible drug interactions for these antimalarial agents.*
4. If a significant interaction has been documented, is there another choice of agent (s) that may be combined instead? *All alternatives should be assessed as above.*

Conclusion

Actual and potential drug interactions with antimalarials are common from both pharmacokinetic and pharmacodynamic perspectives. The body of literature summarized in this book provides insight for researchers and clinicians to assess the significance of these interactions in practice. Although literature was limited in terms of amount available, drug classes studied, and quality of identified studies, knowledge of these interactions is increasing and will continue to increase with more experience using antimalarials in combination with other agents. In light of increased use of chronic disease medications worldwide, future studies should focus on commonly used agents to provide guidance for clinicians and patients when selecting drug therapy. With careful consideration of both patient and drug factors, outcomes can be optimized for both efficacy and safety.

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