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)

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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)

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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)

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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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