

## Review

# A review of clinical pharmacokinetics of chloroquine and primaquine and their application in malaria treatment in Thai population

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The blood schizontocidal chloroquine (CQ) and the tissue schizontocidal and gametocytocidal primaquine (PQ) remain the mainstay treatment of *Plasmodium vivax* and *Plasmodium ovale* infections for more than six decades. The review focuses on the clinical pharmacokinetic studies of both drugs in Thai population that have provided useful information for clinical application in the treatment of malaria. There appears to be no major differences in the pharmacokinetics of both drugs with respect to the influences of ethnicity, acute phase malaria infection, and G6PD status. The increase in systemic exposure of CQ and/or its metabolite mono-desethylchloroquine (DECQ) following oral administration could be due to change in the absorption kinetics during acute phase infection. The high clinical efficacy of CQ for treatment of *P. vivax* infection in Thailand supports this beneficial pharmacokinetic change. Transiently high and toxic plasma/whole blood concentrations of CQ following intravenous infusion at high rate is explained by the pharmacokinetic characteristics of CQ. Pharmacokinetics of PQ following repeated dosing in most studies appears to be similar to that following a single dosing. This suggests that auto-inhibition of PQ metabolism during multiple dosing is unlikely. Co-administration of CQ, dihydroartemisinin-piperaquine (DHA-PIP), and pyronaridine-artesunate (PYR-ARS) significantly altered the pharmacokinetics of PQ. In the presence of these drugs, PQ exposure was significantly increased. The apparent volume of distribution of PQ was reduced when co-administered with PYR-ARS. In addition, plasma concentrations of CPQ were significantly increased in the presence of CQ. Clinical relevance of these interactions needs to be confirmed.

**Key words:** Malaria, pharmacokinetics, chloroquine, primaquine, Thai population.

## INTRODUCTION

Malaria remains a major public health problem in many countries of the world. Despite the progress in reducing malaria cases and deaths, it is estimated that 212 million cases of malaria occurred worldwide in 2015, leading to

429,000 malaria deaths [World Health Organization (WHO), 2016]. Five species of parasites belonging to the genus *Plasmodium* infect humans that is, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*,

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*Plasmodium ovale* and *Plasmodium knowlesi*. All species spread from one person to another via the bite of female mosquitoes of the genus *Anopheles*. *P. falciparum* and *P. vivax* malaria pose the greatest public health challenge. *P. falciparum* is most prevalent in the African continent, and is responsible for most deaths from malaria. *P. vivax* has a wider geographical distribution with about 13.8 million malaria cases globally in 2015 (WHO, 2016). The disease is rarely life-threatening but morbidity from a prolonged illness and the possibility of relapses from a dormant hepatic form (hypnozoite) is of major concern. In Thailand, *P. vivax* infection was the predominant species, accounting for 54% of all malaria cases in 2015 (Bureau of Vector Borne Diseases of Thailand, 2015).

Blood schizontocidal chloroquine (CQ) and tissue schizontocidal primaquine (PQ) remain the mainstay treatment of *P. Vivax*, as well as *P. ovale* infections in Thailand and most of the endemic areas for more than six decades. The wide clinical use of CQ in the treatment of malaria is mainly due to its safety, availability, and affordability. The drug has now been rendered completely ineffective for treatment and prophylaxis of *P. falciparum* due to drug resistance. The clinical efficacy of a three-day CQ for *P. vivax* infection in Thailand is conserved with cure rate of virtually 100% (Tasanor et al., 2006; Vijaykadga et al., 2006; Muhamad et al., 2011), although a trend in gradual decline of *in vitro* sensitivity to the drug has been documented in some areas of the country, particularly along the Thai-Myanmar border (Bureau of Vector Borne Diseases of Thailand, 2015). Nevertheless, the accumulating reports of CQ resistant *P. vivax* in other parts of the world during the past three decades, particularly in Southeast Asian region including Indonesia, Papua New Guinea, Irian Jaya and Vietnam (WHO, 2016), emphasize the need for closely and continuously monitoring clinical efficacy of CQ in conjunction with *in vitro* sensitivity with confirmed adequacy of systemic drug exposure.

The 8-aminoquinoline PQ is the only available drug which rapidly and reliably kills mature gametocytes of *P. falciparum*, and therefore, limits transmissibility of the infection (WHO, 2016). The emergence of artemisinin resistance in *P. falciparum* infection and the drive to completely control malaria have led the WHO to recommend the addition of PQ as a gametocytocidal drug to all artemisinin-based combination therapies (ACTs) to interrupt the transmission and spread of *P. talciparum* infection (WHO, 2016). A single PQ dose of 0.75 mg base/kg body weight or 45-mg adult dose was recommended originally as a gametocytocide in several countries for several years, but a lower dose of 0.25 mg base/kg body weight (15-mg adult dose) has recently been proposed as a safer dose to patients with unknown glucose-6-phosphate dehydrogenase (G6PD) status.

The current review focuses on the clinical pharmacokinetic studies of both drugs in Thai population that have provided useful information for clinical

application in the treatment of malaria. The information on plasma/blood drug concentrations and pharmacokinetic profiles of both the parent drugs and their active metabolites are essential for optimization of dosage regimen of CQ and PQ for the treatment of malaria. The pharmacokinetics of CQ and its active plasma metabolite mono-desethylchloroquine (DECQ) as well as PQ and its major plasma metabolite carboxyprimaquine (CPQ) in Thai population in healthy subjects and patients with malaria from thirteen studies conducted during 1980-2017 are summarized in this review.

Research articles published during 1972-2017 relating to clinical pharmacokinetics of CQ and PQ in healthy subjects or patients with malaria were collected from PubMed database. The published articles on CQ pharmacokinetics included 50 articles in Caucasean (13 articles), Asian (15 articles including 4 articles in Thai subjects) and African (22 articles) ethnics. The published articles on PQ pharmacokinetics included 19 articles in Caucasean (2 articles), Asian (16 articles including 9 articles in Thai subjects) and South American (1 article) ethnics. Furthermore, relevant articles on the pharmacokinetics of CQ and PQ *in vitro* and *in vivo* in other populations were also retrieved from the database. All articles were thoroughly read but the analysis of clinical pharmacokinetics and application for the treatment of malaria was performed only the articles in Thai subjects.

## CLINICAL PHARMACOKINETICS OF CHLOROQUINE IN THAI POPULATIONS

Chloroquine (CQ) [7-chloro-4-diethylamino-1-methylbutylamino) quinoline] is a synthetic antimalarial agent which is a 4-aminoquinoline derivative (Figure 1). Slow, rate-controlled intravenous infusion, is an acceptable mode of CQ administration in seriously ill patients or where oral therapy is not possible (Looareesuwan et al., 1986; Edwards et al., 1987). CQ is generally well tolerated (Ducharme et al., 1996). The main adverse effects reported after therapeutic or prophylactic regimens include nausea, vomiting, abdominal discomfort, diarrhea, headache, blurred vision, lightheadedness, and fatigue. Gastrointestinal disturbance can be minimized by taking the drug with food. Pruritus, especially of the palms and soles occurs frequently in Africans. Transiently high plasma CQ concentrations after the rapid intravenous injection or large intramuscular doses are associated with acute, concentration-dependent cardiovascular toxicity. Toxic manifestations appear rapidly within 1 to 3 h after injection and include circulatory arrest, shock, cardiac conduction disturbances, and ventricular arrhythmia. Abnormality in the electrocardiogram that is QRS complex widening, flattening of the QRS, and ST

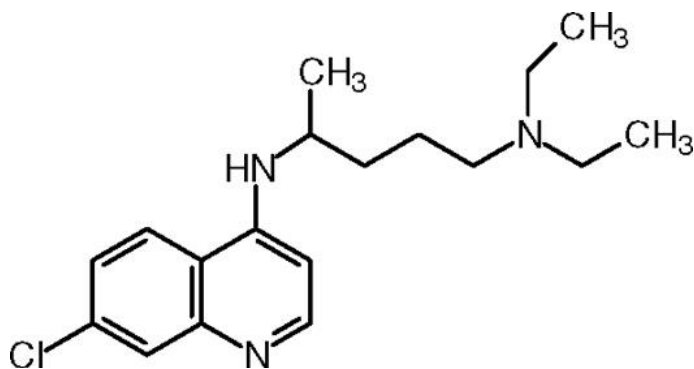


Figure 1. Chemical structure of chloroquine.

segment depression have been reported after overdoses as well as in patients after therapeutic doses. Another arthritis, is irreversible retinopathy. Rare adverse effects are photosensitization, aplastic anemia, agranulocytosis, myopathy, and psychiatric disturbances. Although CQ is generally well tolerated, it has a relatively narrow margin of safety and an overdose (1 g in young children and 4 g in adults) (Krishna and White, 1996) can be fatal.

### General pharmacokinetic properties

The pharmacokinetics of CQ in *P. falciparum* has been well documented in various populations (Krishna and White, 1982; Karbwang et al., 1992; Ducharme et al., 1996). However, such information is rather limited in other types of *Plasmodium* infection including *P. vivax*. CQ is rapidly and almost completely absorbed from the gastrointestinal tract after oral administration (80 to 90% bioavailability) in either healthy subjects or patients with malaria. Following intramuscular and subcutaneous administration, the drug is rapidly and equally well absorbed even in patients with severe malaria. Its pharmacokinetic profile is complicated. Due to its extensive tissue distribution throughout the body, the total volume of distribution is extremely large (100 to 1,000 l/kg body weight) compared with the volume of central compartment (0.2 l/kg body weight) (Krishna and White, 1996). This explains the transiently high blood concentrations and wide peak to trough fluctuation after parenteral administration (Looareesuwan et al., 1986). Approximately 50 to 70% of CQ is bound to plasma protein mainly to  $\alpha_1$ -acid glycoprotein. It readily crosses the placenta and is excreted in small amount into breast milk. CQ is metabolized in liver to mono-desethylchloroquine (DECQ) which is subsequently metabolized to bidesethylchloroquine. The drug is slowly eliminated from the body with multi-exponential elimination pattern that is, a more rapid initial elimination phase, followed by a slower phase. CQ and DECQ can be detected in plasma for up to 56 days. The total

serious adverse effect associated with long-term use of CQ, either as prophylaxis or treatment of rheumatoid clearance of CQ varies between 750 and 1,000 ml/min and the renal clearance is about half of total clearance (400 to 500 ml/min). The kidney is the main route of drug elimination, probably by both glomerular filtration and tubular secretion. CQ is predominantly excreted unchanged (about 50%) in urine, the DECQ accounts for only about 25%.

In general, the pharmacokinetics of CQ does not differ substantially in different ethnic groups including Thai subjects. There appears to be no significant influence of malaria infection on the pharmacokinetics of CQ. In malnourished patients, the metabolism of CQ is impaired. In patients with renal insufficiency, CQ elimination is reduced resulting in the prolongation of the elimination half-life of the drug (Karunajeewa et al., 2010). Pregnancy significantly influences the pharmacokinetics of both CQ and DECQ resulting in low systemic drug exposure which could compromise both curative efficacy and post-treatment prophylactic properties in pregnant patients (Karunajeewa et al., 2010).

Previous studies of CQ and DECQ pharmacokinetics involved small number of subjects and in some cases, with limitation of sensitivity of analytical methods and pharmacokinetic analysis approach (Gustafsson et al., 1987; Tett and Cutler, 1987; Edwards et al., 1988; Titus et al., 1989; Lee et al., 2008; Zhao et al., 2014). In addition, a wide range of inter-individual variability in the estimated pharmacokinetic parameters hinders optimization of dose regimens of CQ particularly in patients infected with *P. vivax*. There were four published articles on the clinical pharmacokinetics of CQ and DECQ in Thai population during 1980-2017 (Table 1). The first two studies investigated the relationship between CQ blood concentrations and cardiovascular adverse effects, as well as the possibility of enhancement of toxicity during acute phase malaria infection due to alteration of pharmacokinetics of CQ/DECQ (Looareesuwan et al., 1986; Edwards et al., 1988). The report on significant impact of acute phase malaria

infection on quinine pharmacokinetics (White et al., 1982) stimulated great concern for clinical use of CQ in patients with malaria. Modification of CQ pharmacokinetics during acute phase malaria infection could aggravate the cardiovascular toxicity of CQ, particularly following intravenous dose administration. During that time, little was known about the disposition of CQ during the acute phase of *P. falciparum* malaria infection. Information of the pharmacokinetics of CQ in patients with malaria is essential for rational and safe intravenous regimens. In another two published articles (Na-Bangchang et al., 1994a; Hoglund et al., 2016), the relationship between clinical efficacy of the standard three-day CQ and the pharmacokinetics of CQ and DECQ were examined in patients with *P. vivax* infection to explain the cause of treatment failure in the light of accumulating evidence for the declining of *in vitro* sensitivity of *P. vivax* isolates in Thailand to CQ.

Looreesuwan et al. (1986) reported a transient but markedly high plasma CQ concentration in a preliminary study in healthy Thai subjects. Edwards et al. (1987) further carried out a detailed study to confirm whether the change in CQ pharmacokinetics during *P. falciparum* infection was also a significant contributing factor to the severe cardiovascular adverse effects following treatment with intravenous administration of CQ. Plasma and red cell concentration-time profiles of CQ in 10 healthy subjects and 9 patients with malaria were analyzed by a non-linear least-squares regression program (NONLIN). Results from both studies suggested that the dangers of intravenous CQ had been exaggerated. Intravenous infusion of CQ at slow rate, for example over 6 to 8 h should be safe and provide adequate plasma/blood CQ concentrations. Transiently high and toxic plasma concentrations of CQ observed after intravenous infusion at high rate (short infusion period) are explained by the pharmacokinetics nature of CQ of which its total apparent volume of distribution (V) is relatively large (about 200 to 1,000-fold) compared with central volume of distribution (V<sub>c</sub>).

Information on the relationship between antimalarial drug concentrations and treatment response is essential for identification of drug target levels and optimization of dosage regimens. For the case of antimalarial drugs, the characterization of the relationship between blood drug concentrations and peripheral blood parasitemia (infected red cell target) is justifiable. The concentrations of CQ and/or its active plasma metabolite DECQ associated with adequate treatment of *P. vivax* malaria remain unclear. Due to extensive binding of CQ and DECQ to blood components particularly red cells, white cells and platelets, a marked variability in their concentrations in whole blood, plasma and serum has been documented. The magnitude of CQ concentrations in descending order is: serum > whole blood > red cells > plasma. Whole blood and red cell CQ concentrations are, respectively

about 3 to 10 and 2 to 5 times higher than the concurrent plasma concentrations. The minimum effective concentration (MEC) of CQ and DECQ in plasma or serum of 15 to 30 ng/ml or in whole blood of 90 to 100 ng/ml has been suggested for treatment of *P. vivax* infection (Baird et al., 1987). The inter-individual variability of the pharmacokinetics of CQ/DECQ could therefore have significant impact on treatment outcome. Inter-individual variability in the pharmacokinetics of CQ/DECQ among different ethnicities has been well documented in patients with *P. falciparum*, but not in *P. vivax* infection.

Clinical efficacy of CQ for treatment of *P. vivax* malaria in Thailand during the past decades up to now remains satisfactory, with cure rate of approximately 100% (Na-Bangchang et al., 1994a; Congpuong et al., 2002; Muhamad et al., 2011). This high efficacy is observed despite an observation of a trend in gradual decline of *in vitro* sensitivity of *P. vivax* isolates to CQ in some areas of the country, particularly along the Thai-Myanmar border (Congpuong et al., 2002; Tasanor et al., 2006; Bureau of Vector Borne Diseases of Thailand, 2015). The relationship between CQ and DECQ blood concentrations and clinical response following the standard three-day regimen of CQ for treatment of *P. vivax* infection was investigated in Thai population in the two studies (Na-Bangchang et al., 1994a; Hoglund et al., 2016). The first conventional pharmacokinetic study was conducted in 7 healthy Thai males (Na-Bangchang et al., 1994a). The purpose of this study was to clarify whether the pharmacokinetic variability in patients with malaria would have been a contributing factor to variability in clinical response following this standard regimen of CQ. The absorption and systemic availability of CQ were higher in patients with *P. vivax* infection compared with healthy subjects as supported by a significantly higher maximal plasma concentration (C<sub>max</sub>) and area under plasma concentration-time curve from time 0 to 28 days of drug administration (AUC<sub>0-28 days</sub>) of CQ, and in addition, the AUC<sub>0-28 days</sub> of DECQ (Table 1). The author concluded that the increase in systemic exposure of CQ and DECQ after oral dosing in patients with malaria could reflect the change in CQ absorption during the acute phase infection since no such change was observed after intravenous dosing (Edwards et al., 1988). This improvement in systemic exposure of CQ/DECQ should benefit treatment of patients, particularly in the light of accumulating reports on increasing level of CQ resistant *P. vivax*. Results of high clinical efficacy of CQ (100%) from various studies in Thailand in larger numbers of patients support this supposition (Muhamad et al., 2011). Since all patients responded well to treatment with no reappearance of parasitemia during the follow up period, relationship between MIC of CQ/DECQ and clinical efficacy could not be assessed in this study.

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**Table 1.** Summary of the pharmacokinetics of chloroquine (CQ) and mono-desethylchloroquine (DECQ) in Thai population.

Reference	Subjects and number	Dose regimen	Summary of PK parameter
Looareesuwan et al. (1985)	12 Healthy males	CQ diphosphate (3 mg base/kg) constant iv infusion over 10 min	<b>CQ</b> C <sub>max</sub> : mean±SD = 2,913±1,434 ng/ml (range = 784-6,649 ng/ml); 1 <sup>st</sup> -order rate constant of the first phase: mean±SD = 0.65±0.14 /min; t <sub>1/2</sub> of decline of the first phase: mean ± SD = 0.133±0.24 /min; 1 <sup>st</sup> -order rate constant of the second phase: 0.133-0.003 /min (range); t <sub>1/2</sub> of decline of the second phase: 5.2-231 /min (range); 1 <sup>st</sup> -order rate constant of the final phase: 0.93-0.029 /day (range); t <sub>1/2</sub> of decline of the final phase: 0.75-23 days (range); V <sub>c</sub> : mean±SD = 0.184±0.145 l/kg; CQ:DECQ ratio at 1 h: 3.6: 1
Edwards et al. (1987)	11 Patients with malaria (10 Pv and 1 Pm) and 10 healthy subjects	CQ diphosphate (15 mg base/kg) constant iv infusion over 4 h	<b>Malaria patients:</b> mean±SD C <sub>max</sub> : 1,693±593 ng/ml; V <sub>c</sub> :0.74±0.75 l/kg; V <sub>ss</sub> :136±64 l/kg; CL:535±246 ml/min; □ <sub>z</sub> : 0.055±0.032 <b>Healthy subjects:</b> mean±SD C <sub>max</sub> : 939±472 ng/ml; V <sub>c</sub> :0.66±0.71 l/kg; V <sub>ss</sub> :132±50 l/kg; CL:597+238 ml/min; □ <sub>z</sub> : 0.062±0.030
Na-Bangchang et al. (1994a)	7 healthy males and 7 Patients with <i>P. vivax</i>	1,500 mg CQ phosphate over 3 days (oral)	<b>Malaria patients:</b> median (range) <b>a. CQ</b> C <sub>max</sub> : 1,547 (996-2,446) ng/ml; AUC <sub>0-28 days</sub> : 281 (250-515) □g.h/ml; t <sub>1/2</sub> : 201 (155-224) h <b>b. DECQ</b> C <sub>max</sub> : 591 (253-761) ng/ml; AUC <sub>0-28 days</sub> : 170 (72-265) □g.hr/ml; t <sub>1/2</sub> : 205 (190-276) h <b>2. Healthy subjects:</b> median (range) <b>a. CQ</b> C <sub>max</sub> : 838 (656-1,587) ng/ml; AUC <sub>0-28 days</sub> : 122 (103-182) □g.r/ml; t <sub>1/2</sub> : 150 (103-266) h. <b>b. DECQ</b> C <sub>max</sub> : 428 (159-637) ng/ml; AUC <sub>0-28 days</sub> : 77 (49-140) □g.h/ml; t <sub>1/2</sub> : 198 (132-329) h
Höglund et al. (2016)	75 patients with <i>P. vivax</i> (8 Thais and 67 Burmeses)	CQ phosphate 25 mg base/kg + PQ 15 mg base/kg for 14 days (start one day after CQ)	<b>Mean (relative standard error: RSE)</b> <b>a. CQ</b> MTT: 0.773 (43.1) h; CL/F: 6.13 (3.4) l/h; V <sub>d</sub> /F: 468 (16) l; V <sub>p</sub> /F: 1,600 (5.21) l; Q/F:: 37.7 (18.9) l/hr; t <sub>1/2</sub> : 10.7 h <b>b. DECQ</b> CL/F: 2.04 (3.5) l/hr; V <sub>d</sub> /F: 2.27 (14.1) l; V <sub>p</sub> /F: 556,257 (14.4) l; Q/F:: 31.46 (12.3) l/hr; t <sub>1/2</sub> : 8.74 h

CQ = chloroquine; DECQ = mono-desethylchloroquine; PQ = primaquine; Pv = *Plasmodium vivax*, Pm = *Plasmodium malariae*; C<sub>max</sub> = maximum plasma/blood concentration; t<sub>max</sub> = time to maximum plasma/blood concentration; V<sub>c</sub> = Volume of distribution of central compartment; V<sub>p</sub> = Volume of distribution of peripheral compartment; V<sub>ss</sub> = Volume of distribution at steady-state; V = Total volume of distribution; t<sub>1/2</sub> = elimination half-life; F = bioavailability; CL = total clearance; MTT = mean transit time; □<sub>z</sub> = terminal phase elimination rate constant; AUC = Total area under plasma/blood concentration-time curve; Q = blood flow.

CQ/DECQ and clinical efficacy of a three-day CQ is a matter of consideration in future studies for continuous monitoring of clinical efficacy of CQ and sensitivity of *P. vivax* isolates in Thailand, in order to maximize the treatment effectiveness as well as to prevent the development of drug resistance. The second study was therefore conducted by our group with the aim to follow

up the change in clinical efficacy of this standard regimen of CQ and its relationship with pharmacokinetics of CQ/DECQ, using population-based pharmacokinetic analysis approach (Höglund et al., 2016). The study was conducted 15 years after the first study in a larger number of patients admitted to Mae Tao clinic for migrant workers in Tak province of Thailand, the area with

multidrug resistant *P. falciparum* along the Thai-Myanmar border. This population-based pharmacokinetic study was also part of the clinical study carried out during 2010-2011 to monitor the clinical efficacy and *in vitro* sensitivity of *P. vivax* isolates to CQ in 75 patients with *P. vivax* malaria (Muhamad et al., 2011). A two-compartment model was best fit with the concentration-time

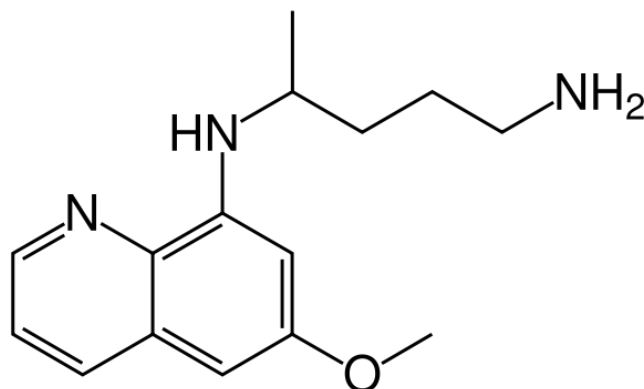


Figure 2. Chemical structure of primaquine.

profiles of both CQ and DECQ, with a one transit compartment model for the absorption of CQ. This multi-exponential decline in blood concentrations of both CQ and DECQ were in consistency with previous reports (Gustafsson et al., 1983; Aderounmu et al., 1986; Karunajeewa et al., 2008; Obua et al., 2008). The mean transit time of absorption (MTT: 0.773 h), peripheral volume of distribution ( $V_p$ : 1,600 l), and elimination half-life ( $t_{1/2}$ : 10.7 days) of CQ were similar to the previously reported values in other populations, but systemic clearance (CL: 6.13 l/h) was relatively lower (Frisk-Holmberg et al., 1984; Aderounmu et al., 1986; Gustafsson et al., 1987; Tett et al., 1987; Edwards et al., 1988; Titus et al., 1989; Vries et al., 1994; Lee et al., 2008; Karunajeewa et al., 2008; Obua et al., 2008; Karunajeewa et al., 2010; Wetsteyn et al., 2012; Zhao et al., 2014). For DECQ on the other hand,  $V_p$  (566,257 l) and CL (2.04 l/h) were relatively lower than the previously reported values. The discrepancies of pharmacokinetic parameters of CQ and DECQ in various studies could be mainly due to difference in sample matrices and pharmacokinetic analysis approaches used. Similar to the previous study (Na-Bangchang et al., 1994a), the MECs of CQ/DECQ could not be determined in this group of patients as none had treatment failure following this standard three-day regimen of CQ. Continuous monitoring is the important key for this matter.

#### CLINICAL PHARMACOKINETICS OF PRIMAQUINE IN THAI POPULATIONS

Primaquine [PQ: 8-(4-amino-1-methyl-butylamino)-6-methoxy-quinoline], (Figure 2) is an 8-aminoquinoline antimalarial that remains the drug of choice for the treatment of exo-erythrocytic stages of *P. vivax* and *P. ovale* since its introduction for more than six decades. It is used as tissue schizontocidal to prevent relapse in combination with the blood schizontocidal CQ. A 14-day course of 15 mg (base) PQ is recommended for the

radical cure of both *P. vivax* and *P. ovale* infections. The drug is also used as a gametocytocidal against *P. falciparum* and is commonly given in combination with standard antimalarials, for example quinine, mefloquine, and ACTs. In Thailand, PQ is currently being used in combination with the three-day artesunate-mefloquine to interrupt the transmission of *P. falciparum*.

#### General pharmacokinetic properties

Absorption of PQ after oral administration in healthy subjects is almost complete with about 70 to 80% bioavailability (Karunajeewa et al., 2010). The apparent volume of distribution is in the range of 100 to 300 l. The concentration-time profiles in whole blood and plasma are similar. PQ is predominantly cleared by hepatic biotransformation. The total clearance is approximately 300 to 600 ml/min with renal clearance of less than 1% (3 to 20 ml/min) of the administered dose over 24 h. Hepatic metabolism of PQ is via monoamine oxidases (A and B), cytochrome P450 (CYP3A4, CYP1A2, and CYP2D6), and flavin-containing monoamine oxygenase 3 enzymes. Several of the identified (for example, CPQ and 6-methoxy-8-aminoquinoline) and unidentified metabolites are detectable in plasma or urine (Constantino et al., 1999; Bennett et al., 2013; Pybus et al., 2013; Jin et al., 2014). The biotransformation pathways important for its therapeutic and toxic effects of PQ remain unclear, but recent evidence suggests that CYP2D6 may play a crucial role in generating the active intermediate metabolites (Constantino et al., 1999; Pybus et al., 2012; Bennett et al., 2013; Jin et al., 2014). The major plasma metabolite CPQ is however unlikely to be directly relevant to antimalarial activity (Pybus et al., 2013). The elimination half-lives of PQ and CPQ range from 3.7 to 9.6 h (Edwards et al., 1993; Cuong et al., 2006; Elems et al., 2006). The pharmacokinetics of both PQ and CPQ are unaffected by dose size within clinically relevant dosage range. Acute *P. falciparum* infection results in a

reduction in the oral clearance of PQ, with no influence on elimination half-life. *P. vivax*, in contrast to *P. falciparum* infection does not significantly influence the disposition of PQ (Edwards et al., 1993; Cuong et al., 2006; Elmes et al., 2006).

PQ and several of its metabolites, 5-hydroxydemethylprimaquine, 5-hydroxyprimaquine and demethylprimaquine have been shown to cause red cell lysis *in vitro* (Fletcher et al., 1988). The serious hemolytic effect of PQ is of great concern especially with concomitant pharmacokinetic drug interactions that could aggravate the effect. The propensity of such pharmacokinetic interaction has been raised when PQ is given at repeated dosing (auto-inhibition of hepatic drug metabolism) as well as in combination with other antimalarial drugs as a tissue schizonticide or gametocytocide. Previous studies demonstrated the potential of PQ as a potent inhibitor of cytochrome P450 in both animals and humans (Back et al., 1983a; Back et al., 1983b; Mihaly et al., 1985; Na-Bangchang et al., 1992). It is thought that the synergistic effects on radical curative activity between PQ and the standard blood schizontocidal antimalarial drugs CQ and quinine (Alving et al., 1980) could be linked to these pharmacokinetic drug interactions (cytochrome P450 inhibition) which result in elevated plasma concentrations of both CQ and quinine.

Most of the early pharmacokinetic studies of PQ and CPQ were conducted in Thai population. This review summarizes findings of the nine pharmacokinetic investigations in relation to the four main issues (Table 2), that is the pharmacokinetic change following multiple dosing of PQ (Greaves et al., 1980; Fletcher et al., 1981; Ward et al., 1985; Singhasivanon et al., 1991), the relationship between patients' G6PD status and PQ and/or CPQ pharmacokinetics (Greaves et al., 1980; Fletcher et al., 1981; Na-Bangchang et al., 1994), the influence of the acute phase malaria infection on pharmacokinetics of PQ, and the pharmacokinetic interactions between PQ and the concurrently administered antimalarial drugs (quinine, chloroquine, mefloquine, dihydroartemisinin-piperaquine, pyronaridine, and artesunate) (Edwards et al., 1993; Na-Bangchang et al., 1994b; Hanboonkunkarn et al., 2014; Jittamala et al., 2015). The first human PQ pharmacokinetic was reported almost concurrently by Greaves et al. (1980) and Fletcher et al. (1981). It is noted however that the pharmacokinetic data presented in the two published articles by the same research group are overlapping (patients included and results reported), with only additional data on methemoglobin levels in 13 Caucasian subjects in the article reported by Fletcher et al. (1981). Plasma kinetics and urinary excretion of PQ following a single oral and multiple dose administration were investigated in 17 healthy subjects (11 Thai and 6 Caucasian subjects) (Alving et al., 1990). In the single

oral dose study, 6 G6PD positive and 5 G6PD negative Thai subjects (weighing 44 to 64 kg) received a single oral dose of 45 mg (base) PQ phosphate, and a total of 8 blood samples were collected over 24 h period. In the multiple dose study, 3 Thai subjects (unidentified G6PD status) received multiple dosing of PQ at 15 mg base for 5 days following previous treatment (one week before) with a three-day CQ (1,500 mg base over 3 days). A total of 8 blood samples were collected on the last day of PQ dosing and plasma PQ concentrations were measured using GC/MS (Greaves et al., 1979). Urinary data were not available for the Thai subjects. The drug was completely or almost completely removed from the plasma within 24 h in all subjects with mono-exponential decline. The urinary excretion of PQ over 24 h was less than 1% of the dose. The following studies (Pybus et al., 2013; Jin et al., 2014) supported hepatic metabolism as the main elimination route of PQ. G6PD status did not influence the pharmacokinetics of PQ and vice versa. No marked difference in the pharmacokinetics of PQ was observed between the Thai and the Caucasian healthy subjects. There was no accumulation of plasma PQ concentrations over the 5 days of dosing. Pre-treatment with CQ did not significantly alter the pharmacokinetics of PQ despite the relatively high systemic exposure of CQ (approximately 500 to 3,000 ng/ml) (Na-Bangchang et al., 1994a; Høglund et al., 2016).

The PQ pharmacokinetics in G6PD-deficient patients with *P. vivax* malaria was in broad agreement with other reports (Greaves et al., 1980; Fletcher et al., 1981; Mihaly et al., 1985; Ward et al., 1985; Bhatia et al., 1986; Na-Bangchang et al., 1994b). After absorption from gastrointestinal tract, the drug rapidly declined mono-exponentially with complete elimination within 24 h of dosing. The undetectable plasma PQ concentration at 24 h throughout a daily dosing for 14 days suggested absence of drug accumulation following repeated doses. This result supported the earlier studies by Greaves et al. (1980), Fletcher et al. (1981) and Bhatia et al. (1986) that auto-inhibition of PQ metabolism during multiple dosing is unlikely despite the evidence that it is a strong inhibitor of hepatic microsomal enzymes. Prior treatment with CQ did not affect the pharmacokinetics of PQ suggesting that the inhibitory effect of CQ on PQ metabolism was unlikely. No relationship between PQ pharmacokinetics and severity of hemolysis (<20% or >20%) was found.

Results from this study in patients with *P. vivax* infection together with the previous study in healthy subjects (Greaves et al., 1980) suggest that the defect in host red cells (G6PD status) rather than PQ and/or its metabolites is a major contributor of the hemolytic effects of PQ. It appeared that *P. vivax* in contrast to *P. falciparum* infection did not affect the disposition of PQ. Bhatia et al. (1986) also reported comparable pharmacokinetics of PQ during the acute phase (day 1) and after recovery (day 14) in Indian patients with *P. vivax*

**Table 2.** Summary of the pharmacokinetics of primaquine (PQ) and carboxyprimaquine (CPQ) in Thai population.

Reference	Subjects and number	Dose regimen	Summary of PK parameters
Greaves et al. (1980) and Fletcher et al. (1981)	11 Healthy Thais (6 G6PD positive and 5 G6PD negative)	A single oral dose of 45 mg base PQ (n=11)	G6PD positive: Mean±SD (range) ke: 0.19±0.04 (0.15-0.26) /h; t1/2: 3.7±0.7 (2.7-4.5) h; AUC: 1,682±455 (1,009-2,204) ng.h/ml; V/F: 149±28 (11-172) l; CL/F: 28.7±8.9 (20.4-44.6) l/h G6PD negative: Mean±SD (range) ke: 0.12±0.04 (0.081-0.17) /h; t1/2: 6.2±1.8 (4.2-8.6) h; AUC: 1,978±789 (1,227-3,219) ng.h/ml; V/F: 226±11 (84-382) l; CL/F: 24.7±4.6 (22.3-34.4) l/h
		Multiple oral dose of 15 mg base for 5 days (n=3)	Individual values: ke: 0.17, 0.12, 0.17 /h; t1/2: 4.0, 6.0, 4.0 h; AUC: 808, 593, 933 ng.h/ml; V/F: 320,660, 280 l; CL/F: 55.7, 75.9, 48.3 l/h
Wards et al. (1985)	5 Healthy Thai males	A single oral dose of 15 mg base	Single dose: mean±SD a. PQ: tmax: 2+1 h; Cmax: 65+34 ng/ml; t1/2: 4.4±1.4 h; CL: 37.6±15.15 l/h AUC: 468+ 229 ng.hr/ml b. CPQ: tmax: 8+2 h; Cmax: 736±236 ng/ml; AUC0-24 h: 14.2± 5.3 ng.h/ml
		Multiple oral dose of 15 mg base daily for 14 days	Multiple doses: mean±SD a. PQ: tmax: 2+1 h; Cmax: 66+27 ng/ml; t1/2: 4.3+1.5 h; CL: 41.2+21.0 l/h; AUC: 443+ 233 ng.h/ml b. CPQ: tmax: 5+2 h; Cmax: 1,240±568 ng/ml; AUC0-24 h: 24.7± 12.0 ng.h/ml
Singhasivanont et al. (1991)	4 Healthy Thai males and 4 healthy Thai females	Multiple oral dose of 15 mg base daily for 14 days	Whole blood PK: Males: a. First-dose tmax: 3.0+0.82 h; Cmax: 77.5+15.54 ng/ml; t1/2: 5.78+1.34 h; CL/F: 0.166+0.066 ml/min/kg; V/F: 121.51+72.35 l; AUC: 742.28+ 211.40 ng.hr/ml a. Last-dose tmax: 1.88+0.75 h; Cmax: 88.75+36.14 ng/ml; t1/2: 4.92+0.58 h; CL/F: 0.210+0.094 ml/min/kg; V/F: 206.24+57.48 l; AUC: 552.15+ 176.59 ng.h/ml
			Females: a. First-dose tmax: 2.5+0.58 h; Cmax: 170.0+62.85 ng/ml; t1/2: 6.06+2.08 hr; CL/F: 0.24+0.065 ml/min/kg; V/F: 100.32+60.41 l; AUC: 1,551.93+ 782.64 ng.h/ml a. Last-dose tmax: 2.62+1.11 h; Cmax: 156.25+85.38 ng/ml; t1/2: 5.85+2.08 hr; CL/F: 0.326+0.089 ml/min/kg; V/F: 171.12+22.74 l; AUC: 1,267.84+ 689.92 ng.h/ml
			Plasma PK: Males: a. First-dose



Table 2. Contd.

		<p>tmax: 2.75+0.96 h; Cmax: 138.75+37.50 ng/ml; t1/2: 6.95+1.94 h; CL/F: 0.149+0.068 ml/min/kg; V/F: 87.36+58.38 l  AUC: 1,307.19+ 522.29 ng.h/ml</p> <p>a. Last-dose  tmax: 2.00+0.71 h; Cmax: 148.75+78.57 ng/ml; t1/2: 6.89+1.70 h; CL/F: 0.180+0.092 ml/min/kg  V/F: 144.98+43.29 l; AUC: 1,153.49+ 577.19 ng.h/ml</p> <p>Females:  a. First-dose  tmax: 3.19+1.07 h; Cmax: 252.50+56.35 ng/ml; t1/2: 4.47+1.40 h; CL/F: 0.11+0.02 ml/min/kg; V/F: 50.79+11.78 l; AUC: 1,900.20+ 298.18 ng.h/ml</p> <p>a. Last-dose  tmax: 2.12+0.63 h; Cmax: 205.00+95.66 ng/ml; t1/2: 4.50+0.91 h; CL/F: 0.189+0.094 ml/min/kg; V/F: 126.34+43.67 l; AUC: 1,356.82+546.55 ng.h/ml</p>
	A single oral dose of 45 mg base PQ	<p>PQ + MQ interaction:  PQ alone:</p>
	A single oral dose of 10 mg/kg MQ	<p>a. PQ  tmax: 2 (1-4) h; Cmax: 167 (113-532) ng/ml; t1/2: 6.1 (1.7-16.1) hr; CL/F: 33.1 (17.6-49.3) l/h</p> <p>b. CPQ:  tmax: 3 (3-16) h; Cmax: 890 (553-3,634) ng/ml; AUC0-24 hr: 12,737 (6,837-27,388) ng.h/ml</p> <p>PQ + MQ:  a. PQ  tmax: 3 (2-4) hr; Cmax: 229 (114-503) ng/ml; t1/2: 3.9 (1.7-13.5) h; CL/F: 34.0 (21.7-49.0) l/h</p> <p>b. CPQ  tmax: 8 (2-24) hr; Cmax: 1,035(174-3,015) ng/ml; AUC0-24 h: 13,471 (2,132-17,863) ng.h/ml</p>
Edwards et al. (1987)	9 Healthy Thai males and 7 Thai male patients with Pf	<p>Effect of malaria infection:  Malaria infection:  a. PQ:  tmax: 4 (2-8) h; Cmax: 233 (144-489) ng/ml; t1/2: 4.9(2.8-9.1) h; C/F: 19.4 (9.3-24.7) l/h</p> <p>b. CPQ:  tmax: 4 (0.5-8) h; Cmax: 345(145-580) ng/ml; AUC0-24 h: 4,306 (1,680-12,030) ng.h/ml</p> <p>Recovery phase + QN:  a. PQ  tmax: 2 (1.5-4) h; Cmax: 295 (64-308) ng/ml; t1/2: 5.1 (1.4-11.6) hr; CL/F: 21.3 (15.9-73.0) l/h</p> <p>b. CPQ  tmax: 4 (1.5-24) h; Cmax: 343(185-875) ng/ml; AUC0-24 h: 3,831 (2,144-15,882) ng.h/ml</p>
	Multiple oral dose of 10 mg QN every 8 hours for 7 days	<p>Convalescence phase:  a. PQ  tmax: 3 (1.5-4) h; Cmax: 271 (147-431) ng/ml; t1/2: 3.5 (2.7-7.9) h; CL/F: 24.8 (12.6-48.4) l/h</p> <p>b. CPQ  tmax: 8 (3-24) h; Cmax: 600 (380-1,055) ng/ml; AUC0-24 h: 7,533 (4,876-18,545) ng.h/ml</p>

Table 2. Contd.

			G6PD normal: mean +SD tmax: 2.2+0.6 h; Cmax: 57.7+7.7 ng/ml; CL/F: 8.54+1.37 ml/min/kg; Vz/F: 4.8+1.7 l/kg; t1/2: 6.4+1.9 h; MRT: 6.8+0.4 h; AUC: 0.547+0.07 ng.h/ml G6PD deficient: mean +SD < 20% hemolysis tmax: 2.3+0.8 h; Cmax: 54.8+5.9 ng/ml; CL/F: 8.93+1.11 ml/min/kg; V/F: 5.5+1.4 l/kg; t1/2: 7.15+2.26 h; MRT: 6.9+0.5 h; AUC: 0.525+0.079 ng.h/ml > 20% hemolysis tmax: 2.0+0 h; Cmax: 56.5+8.8 ng/ml; CL/F: 9.01+1.79 ml/min/kg; V/F: 4.8+1.2 l/kg; t1/2: 6.4 +1.9 h; MRT: 6.7+0.5 h; AUC: 0.517+0.103 ng.h/ml
Na-Bangchang et al. (1994b)	26 Thai males with Pv (13 G6PD positive and 13 G6PD negative)	Multiple oral dose of 15 mg base daily for 14 days	
		A single oral dose of 30 mg base PQ	Effect of PQ on DHA and PIP PKs: [median (range)] DHA-PIP alone  a.DHA tmax: 1.5 (1-6) h; Cmax: 364 (184-792) ng/ml; CL/F: 2.21 (0.96-5.01) l/h/kg; V/F: 5.53 (2.67-11.3) l/kg; t1/2: 1.97 (1.13-2.67) h; AUC: 817 (398-2,030) ng.h/ml b. PIP tmax: 4.0 -(3-4) h; Cmax: 491 (129-1,270) ng/ml; CL/F: 0.450 (0.17-0.73) l/h/kg; V/F: 225 (120-593) l/kg; t1/2: 390 (224-669) h; AUC: 20,400 (11,400-57,300) ng.h/ml DHA-PIP + PQ a. DHA tmax: 1.5 (0.5-3) h; Cmax: 348 (194-961) ng/ml; CL/F: 2.23 (0.87-5.52) l/h/kg; V/F: 5.89 (2.70-11.0) l/kg; t1/2: 1.81 (1.13-2.84) hr; AUC: 899 (361-2,250) ng.h/ml b. PIP tmax: 4.0 (3-6) h; Cmax: 397 (127-1,200) ng/ml; CL/F: 0.441 (0.275-0.554) l/h/kg; V/F: 265 (139-339) l/kg; t1/2: 449 (206-610) h; AUC: 19,800 (15,400-35,900) ng.h/ml Effect of DHA and PIP on PQ PK: [median (range)] PQ: tmax: 1.79 (0.5-3) h; Cmax: 128 (20.2-249) ng/ml; CL/F: 0.403 (0.173-2.98) l/hr/kg; V/F: 4.19 (2.46-19.3) l/kg; t1/2: 6.78 (4.45-9.84) h; AUC: 1,130 (149-2,830) ng.h/ml
Hanboonkunupakam et al. (2014)	16 Healthy Thais (5 males and 11 females)	A single oral dose of DHA-PIP (120/960 mg)	
		A single oral dose of 30 mg base PQ	Effect of CQ on PQ/CPQ PKs: median(range) PQ alone: (n=16)  a. PQ tmax: 3.0 (1-3) h; tlag: 0.25 (0-0.5) h; Cmax: 122 (50.1-215) ng/ml; CL/F: 25.3 (13.0-53.0) l/h; V/F: 247 (154-544) l; t1/2: 6.63 (5.10-10.3) h; AUC: 1,190 (566-2,310) ng.h/ml b. CPQ tmax: 8.0 (4-12) h; tlag: 0.25 (0-0.5) h; Cmax: 1,080 (650-1,420) ng/ml; CL/F: 0.560 (0.102-0.862) l/h; V/F: 25.6 (19.6-43.6) l; t1/2: 33.2 (20.4-165) h; AUC: 56,700 (36,800-312,000) ng.h/ml PQ + CQ: (n=16)
Phukrittayakamee et al. (2014)	16 Healthy Thais (4 males and 12 females)	A single oral dose of 600 mg CQ	

**Table 2.** Contd.

			<p>a. PQ  <math>t_{max}</math>: 2.0 (0.50-4.0) h; <math>t_{lag}</math>: 0.25 (0-0.5) h; <math>C_{max}</math>: 208 (109-424) ng/ml; CL/F: 20.9 (11.3-31.5) l/hr; V/F: 162 (96.5-271) l; <math>t_{1/2}</math>: 5.90 (4.11-7.80) h; AUC: 1,440 (953-2,630) ng.h/ml</p> <p>b. CPQ  <math>t_{max}</math>: 8.0 (4-12) h; <math>t_{lag}</math>: 0 (0-0.5) h; <math>C_{max}</math>: 1,300 (987-1,660) ng/ml; CL/F: 0.549 (0.328-0.899) l/h; V/F: 21.5 (14.6-27.6) l; <math>t_{1/2}</math>: 24.8 (12.9-45.9) h; AUC: 57,900 (35,300-96,800) ng.h/ml</p> <p>Effect of PQ on CQ/DECQ PKs: median(range)  CQ alone: (n=16)</p> <p>a. CQ  <math>t_{max}</math>: 3.0 (1-6) h; <math>t_{lag}</math>: 0.25 (0-0.5) h; <math>C_{max}</math>: 295 (110-496) ng/ml; CL/F: 40.0 (24.5-56.5) l/h; V/F: 7,600 (4,450-12,400) l; <math>t_{1/2}</math>: 134 (82.9-329) h; AUC: 15.0 (10.6-24.5) mg.h/ml</p> <p>b. DECQ  <math>t_{max}</math>: 35.2 (1-143) h; <math>t_{lag}</math>: 0.75 (0.25-1.5) h; <math>C_{max}</math>: 73.7 (33.6-121) ng/ml; CL/F: 34.6 (18.3-87.6) l/h; V/F: 13,000 (7,540-61,000) l; <math>t_{1/2}</math>: 312 (88.7-1,200) h; AUC: 15.8 (6.25-29.9) mg.h/ml</p> <p>CQ + PQ: (n=16)</p> <p>a. CQ  <math>t_{max}</math>: 2.0 (1-6) h; <math>t_{lag}</math>: 0.25 (0-0.5) h; <math>C_{max}</math>: 290 (166-650) ng/ml; CL/F: 37.6 (21.4-52.9) l/h; V/F: 9,170 (5,850-33,400) l; <math>t_{1/2}</math>: 168 (85.4-615) h; AUC: 16.0 (11.3-28.0) mg.h/ml</p> <p>b. DECQ  <math>t_{max}</math>: 9.0 (1.5-71.0) h; <math>t_{lag}</math>: 0.50 (0.25-1.5) h; <math>C_{max}</math>: 56.4 (33.9-152) ng/ml; CL/F: 43.2 (15.8-123) l/h; V/F: 17,700 (6,370-54,100) l; <math>t_{1/2}</math>: 295 (86.6-2,380) h; AUC: 12.7 (4.47-34.7) mg.h/ml</p>
		A single oral dose of 30 mg base PQ	<p>Effect of PQ on PYR PK: [median (range)]  PYR alone:</p> <p>a. PYR  <math>t_{max}</math>: 1.5 (1-6) h; <math>C_{max}</math>: 341 (256-571) ng/ml; CL/F: 38.8 (22.5-48.5) l/h; V/F: 25,100 (9,370-44,100) l; <math>t_{1/2}</math>: 397 (262-635) h; AUC : 13,900 (11,100-24,000) ng.h/ml</p> <p>b. PYR + PQ  <math>t_{max}</math>: 1.55 (1-10) h; <math>C_{max}</math>: 366 (223-783) ng/ml; CL/F: 39.9 (20.1-52.2) l/hr; V/F: 20,500 (9,410-35,400) l; <math>t_{1/2}</math>: 333 (246-732) h; AUC: 13,500 (10,300-26,900) ng.h/ml</p> <p>.Effect of PQ om ARS/DHA PK: [median (range)]  ARS alone:</p> <p>a. ARS  <math>t_{max}</math>: 1.0 (0.5-2.05) h; <math>C_{max}</math>: 82.6 (34.2-340) ng/ml; CL/F: 1,670 (1,170-4,020) l/h; V/F: 1,920 (326-5,890) l; <math>t_{1/2}</math>: 0.7 (0.143-1.97) h; AUC: 144 (59.7-206) ng.h/ml</p> <p>b. DHA  <math>t_{max}</math>: 1.70 (0.5-3.0) h; <math>C_{max}</math>: 523 (311-1,380) ng/ml; CL/F: 125 (64.7-202) l/h; V/F: 303 (188-524) l; <math>t_{1/2}</math>: 1.86 (1.15-2.50) h; AUC : 1,420 (879-2,760) ng.h/ml</p> <p>ARS + PQ:</p> <p>a. ARS  <math>t_{max}</math>: 1.0 (0.25-2.5) h; <math>C_{max}</math>: 119 (23.5-370) ng/ml; CL/F: 1,680 (827-4,730) l/h; V/F: 1,440 (516-4,960) l; <math>t_{1/2}</math>: 0.568 (0.313-1.52) h; AUC : 143 (50.7-290) ng.h/ml</p>
Jittamala et al. (2015)	17 Healthy Thais (8 males and 9 females)	A single oral dose of PYR-ARS (180:60)	

Table 2. Contd.

	<p>b. DHA  tmax: 1.50 (0.5-3.0) h; Cmax: 616 (250-1,760) ng/ml; CL/F: 108 (63-192) l/h; V/F: 255 (156-571) l; t1/2: 1.72 (1.02-3.52) h;  AUC: 1,650 (923-2,800) ng.h/ml  Effect of PYR on PQ/CPQ PK: [median (range)]  PQ alone:</p> <p>a. PQ  tmax: 2.0 (1.5-6.0) h; Cmax: 139 (107-242) ng/ml; CL/F: 25.4 (14.7-43.6) l/h; V/F: 218 (126-326) l; t1/2: 6.07 (4.53-8.22) h;  AUC: 1,180 (688-2,050) ng.h/ml</p> <p>b. CPQ  tmax: 8.02 (4-12) h; Cmax: 1,040 (665-1,460) ng/ml; CL/F: 0.670 (0.460-1.33) l/h; V/F: 22.8 (15.5-32.4) l; t1/2: 21.3 (16.8-29.4) h; AUC : 47,200 (23,900-69,000) ng.h/ml</p> <p>PQ + PYR:</p> <p>a. PQ  tmax: 1.5 (1-3) h; Cmax: 192 (112-340) ng/ml; CL/F: 20.4 (10.4-43.6) l/h; V/F: 174 (93.2-253) l; t1/2: 5.81 (3.89-8.94) h; AUC: 1,470 (687-2,890) ng.h/ml</p> <p>b. CPQ  tmax: 8.0 (3-12) h; Cmax: 1,100 (718-1,750) ng/ml; CL/F: 0.720 (0.389-1.46) l/h; V/F: 20.5 (12.9-29.3) l; t1/2: 18.0 (13.9-27.0) h  AUC : 44,100 (21,800-81,500) ng.h/ml</p>
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ARS=Artesunate; CQ = chloroquine; DHA = dihydroartemisinin; MQ=mefloquine; PIP = piperazine; PQ = primaquine; PYR=pyronaridine; QN = quinine; C<sub>max</sub> = maximum plasma/blood concentration; t<sub>max</sub> = time to maximum plasma/blood concentration; t<sub>lag</sub> = Absorption lag time; V<sub>c</sub> = Volume of distribution of central compartment; V<sub>p</sub> = Volume of distribution of peripheral compartment; V<sub>ss</sub> = Volume of distribution at steady-state; V = Total volume of distribution; t<sub>1/2</sub> = elimination half-life; F = bioavailability; CL = total clearance; MTT = mean transit time; MRT = mean residence time; λ<sub>z</sub> = terminal phase elimination rate constant; AUC = Total area under plasma/blood concentration-time curve; AUC<sub>0-24h</sub> = Area under plasma/blood concentration-time curve during time zero until 24 h; Q = blood flow.

infection. The observed systemic clearance was similar to that reported in healthy Thai and Caucasian subjects (Greaves et al., 1980; Mihaly et al., 1985; Fletcher et al., 1981).

The potential of PQ to alter its own disposition, and in addition, accumulation of plasma concentrations of the carboxylic acid metabolite CPQ during repeated dosing was further investigated in 5 healthy Thai male subjects by Ward et al. (1985) at Trang Provincial Hospital, southern Thailand. The study design was a cross-over design in which each subject received PQ on two occasions, that is a single oral dose of 15 mg (base) PQ on the first occasion and repeated oral dose of 15 mg (base) daily for 14 days (no

information on pharmaceutical formulation of PQ provided). Frequent blood samplings (20 time points) were collected during the first 24 h and additionally on day 14 of multiple dosing. Additional blood samples were obtained 3 h after the morning dose of each day between day 1 and 13. PQ and CPQ plasma concentrations at 3 h after dosing were used as markers for assessing patients' compliance to the prescribed dosage schedule of multiple dosing. Pharmacokinetic data analysis was performed using model-independent approach. Patients' compliance to multiple dosing of PQ was 100%. There appears to be no influence of ethnics on the pharmacokinetics of PQ and CPQ. The pharmacokinetics of both

compounds were generally in agreement with that reported in healthy Caucasian subjects (Back et al., 1983a). Multiple oral dosing of PQ had no effect on the pharmacokinetics of PQ when compared with that following a single oral dose. On the other hand, plasma concentrations of CPQ accumulated after chronic dosing as illustrated by the 74% increase in the area under plasma concentration-time profile from time 0 to 24 h of drug administration (AUC<sub>0-24h</sub>) and the 68% increase in C<sub>max</sub> of CPQ on day 14 of PQ dosing (Table 2). The therapeutic implication of this accumulation particularly in patients with malaria needs to be evaluated.

The issue of pharmacokinetic alteration after

repeated therapeutic doses was further studied by Singhasivanon et al. (1991) in 8 healthy subjects. The pharmacokinetic profile of PQ was generally in broad agreement with other reports (Mihaly et al., 1985; Ward et al., 1985; Na-Bangchang et al., 1994b).

The concentration-time profiles in whole blood and in plasma were similar. It was noted for a wide inter- as well as intra-individual variability in the pharmacokinetics of PQ in this group of subjects. Whole blood and plasma  $C_{max}$  of CQ were significantly higher in female compared with male subjects following the first dose of PQ. A significant increase in total clearance of PQ was found following the last dose leading to the observed lower AUC and  $C_{max}$  compared with that after the first dose (Table 2). These findings were in contrast with the previously described studies by Mihaly et al. (1985), Greaves et al. (1980), and Ward et al. (1985) in which similar total body clearance with no accumulation of PQ was found after multiple dose administration of 15 mg PQ. The pre-dose plasma PQ concentrations at steady in this study varied from 0 to 35 ng/ml while Greaves et al. (1980) reported undetectable level. The change in bioavailability due to the consumption of carbohydrate-rich meals, rather than the auto-inhibitory effect of PQ was explained as the cause of the observed low bioavailability of PQ. The effect of food on PQ absorption remains to be clarified.

The propensity of most antimalarial drugs to inhibit hepatic drug metabolizing enzymes had previously been reported in various studies (Back et al., 1983a; Back et al., 1983b; Mihaly et al., 1985; Riviere and Back, 1985; Na-Bangchang et al., 1992). Clinically relevant drug interaction was of a great concern when PQ is to be given concurrently with other antimalarial drugs. Moreover, malaria infection was also reported to alter hepatic drug metabolism and pharmacokinetics of several antimalarial drugs both *in vitro* and *in vivo* (Back et al., 1983b; Mansor et al., 1990; Edwards et al., 1993). The issues of pharmacokinetic drug interactions between PQ and the concurrently administered antimalarial drugs and influence of malaria infection on the pharmacokinetics of PQ were clarified in the following four studies conducted in Thai subjects (Edwards et al., 1993; Mansor et al., 1990; Hanboonkunupakarn et al., 2014; Jittamala et al., 2015). Edwards et al. (1993) investigated the pharmacokinetics of PQ and CPQ when given in combination with mefloquine and with quinine in 9 healthy Thai subjects and 14 *P. falciparum* patients. PQ was rapidly absorbed in both groups of subjects (Table 2). Administration of a single oral dose of MQ in healthy subjects had no effect on the pharmacokinetics of both PQ and CPQ including the biotransformation of PQ to CPQ (mean ratio of  $CL_{mefloquine}: CL_{Control} = 1.09$ ). In patients with *P. falciparum* infection, all patients responded well to treatment with the standard 7 days quinine with no apparent adverse drug reactions. Acute falciparum malaria was associated with a significant

decrease in oral clearance (CL/F) of PQ from 21.3 (15.9 to 73.0) to 19.4 (9.3 to 24.7) l/h. This was explained by an impairment of hepatic drug metabolizing enzymes or a reduction in absorption across the gastrointestinal wall, or both. With regards to drug-drug interactions, while mefloquine did not significantly influence the biotransformation of PQ to CPQ (mean ratio of  $CL_{mefloquine}: CL_{Control} = 1.09$ ), the biotransformation of PQ was influenced by quinine. The mean ratio AUC<sub>0-24h</sub> of PQ during convalescence (without quinine dosing) and during recovery (with quinine dosing) was 3.23. The AUC<sub>0-24h</sub> of CPQ was significantly larger following PQ alone compared with PQ in combination with quinine (Table 2). The mechanism(s) involved and its clinical significance remain to be elucidated.

The pharmacokinetic interaction between the tissue schizonticide PQ and the blood schizonticide CQ was investigated in 16 healthy Thai adults (Phukrittatakamee et al., 2014). Pharmacokinetic assessment was performed with a model-independent approach. The pharmacokinetics of PQ was generally in agreement with the previously reported values. Co-administration of a single oral dose of CQ significantly influenced the pharmacokinetics of PQ, while PQ had only negligible effects on the disposition of CQ. In the presence of CQ, a 63% increase in  $C_{max}$  for PQ + CQ and PQ alone, respectively and a 24% increase in total exposure (AUC) of PQ were found (Table 2). The adverse effect of CQ on prolongation of electrocardiographic QTc interval (White, 2007) was not affected by PQ. In a previous study (Edwards et al., 1993), pre-treatment with a three-day CQ regimen did not affect the pharmacokinetics of PQ. The reduced CYP2D6-mediated PQ metabolism together with reduced apparent volume of distribution of PQ could explain the relatively greater effect on  $C_{max}$  than AUC or elimination rate. This pharmacokinetic interaction appeared to correlate well with the pharmacodynamic interaction resulting in the synergistic effect of both drugs on antimalarial activity particularly on the hypnozoite stage (Alving et al., 1990). The authors concluded that the potentiation of the radical curative activity of PQ by CQ is likely to be a pharmacokinetic rather than pharmacodynamic basis since CQ completely lacks hypnozoitocidal activity (White, 2007). Whether CQ potentiates the hemolytic toxicity of PQ in G6PD-deficient patients remains to be investigated.

Artemisinin-based combination therapy (ACT) is currently the recommended first-line treatment for uncomplicated *P. falciparum* malaria in all malaria endemic areas (WHO, 2016). In areas with low transmission, it is recommended that ACTs should be administered in combination with the gametocytocidal drug PQ to decrease the risk of spreading artemisinin resistance (WHO, 2016). The fixed-dose combination of dihydroartemisinin and piperazine phosphate (DHA-PIP) is also being used increasingly for the treatment of *P. vivax* infection, particularly in areas where CQ resistance

is prevalent (Leang et al., 2016; WHO, 2016). The normal adult dose is three tablets of DHA-PIP (40 and 320 mg per tablet) given once daily for 3 days (WHO, 2016). The use of DHA-PIP together with PQ in the treatments of both *P. falciparum* and *P. vivax* infections raised concern about the propensity of pharmacokinetic drug interactions. Hanboonkunuprakarn et al. (2008) conducted a study to investigate possible pharmacokinetic interaction between DHA-PIP in 16 healthy Thai adults (5 males and 11 females, aged 18 to 60 years, and weighing 54 to 71.4 kg) in a prospective, randomized, crossover study at the Hospital for Tropical Diseases, Mahidol University. The volunteers were randomized to two groups of three sequential hospital admissions to receive a single oral dose of (i) 30 mg (base) PQ (PQ phosphate, 15 mg base per tablet, GPO) alone, (ii) 3 tablets of DHA-PIP (120/960 mg, Eurartesim™, Sigma-Tau Industrie Farmaceutiche Riunite SPA) alone, and (iii) combination of PQ and DHA-PIP at the same doses. Blood samples were collected over 3 days following PQ and 36 days following DHA-PIP dosing. The washout periods between doses following PQ and DHA-PIP were  $\geq 1$  week and  $\geq 8$  weeks, respectively. Pharmacokinetic data analysis was performed using a model-independent analysis approach. All study drugs were found to be well tolerated. The pharmacokinetics of DHA-PIP in the presence or absence of PQ was comparable. On the other hand, DHA-PIP co-administration significantly increased plasma PQ concentrations. The geometric mean ratios [90% confidence interval (CI)] of PQ  $C_{max}$  was significantly increased by 148 (117 to 187)%, while AUC was increased by 128 (102 to 161)%. This interaction is similar to that previously described for CQ and PQ and similar mechanism of pharmacokinetic as well as pharmacodynamic interaction on enhanced radical curative effect would be expected.

A fixed-dose combination of pyronaridine and artesunate (PYR-ARS) is the only ACT that is registered for treatment of both *P. falciparum* and *P. vivax* infections (Ringwald et al., 1999). Previous studies showed that both pyronaridine and PQ may share the same metabolic pathways, particularly CYP2D6-mediated metabolism (Li et al., 2003) and the potential pharmacokinetic drug interactions could have important therapeutic implications. Hepatic clearance of pyronaridine is via CYP1A2-, CYP2D6-, and CYP3A4-mediated metabolism. The drug has also been reported to be a potent inhibitor of CYP2D6, a moderate inhibitor of CYP1A2, and a weak inhibitor of CYP3A4 (Li et al., 2003).

Jittamala et al. (2015) conducted an open-label, randomized, and single-dose study in 17 healthy adult Thai subjects (8 males and 9 females, aged 20 to 49.4 yr, weighing 47 to 64 kg) at the Hospital for Tropical Diseases, Mahidol University. The aim of the study was to investigate the potential pharmacokinetic and pharmacodynamic (safety and tolerability) between PYR-

ARS and PQ. The volunteers were randomized into two groups (A and B) without stratification by gender. All received PQ alone on the first occasion. Subjects in group A (n = 8) and B (n = 8) received PYR-ARS and PYR-ARS plus PQ on the second occasion, and vice versa during the third occasion. The washout period between each occasion was at least 7 days after PQ alone and at least 8 weeks after PYR-ARS. Pharmacokinetic analysis was performed using model-independent approach followed by bioequivalence evaluation. All study drugs were well tolerated. Adverse effects reported included nausea and elevated levels of direct and total bilirubin. The pharmacokinetics of all drugs were in close agreement with those previously reported (Navaratnam et al., 2000; Morris et al., 2011). The single oral dose of PQ did not result in any clinically relevant pharmacokinetic alterations to PYR, AS, or DHA exposures. On the other hand, co-administration of PYR-ARS with PQ significantly reduced the apparent volume of distribution of PQ by 20%, with a subsequent increase in total PQ exposure (AUC) by 15%. It was proposed that displacement of tissue binding or decrease of PQ absorption was the possible mechanisms of the interaction. The observation of slight decrease in PQ clearance may have been due to the inhibition of CYP2D6 and/or CYP3A4. AS has a very short elimination half-life (approximately 1 h) as it is rapidly metabolized by esterase-catalyzed hydrolysis and hepatic CYP2A6 into DHA, which is subsequently metabolized by UGTs1A9 and 2B7 to glucuronide metabolites (Navaratnam et al., 2000; Morris et al., 2011). These results were consistent with the previous reports showing a similar interaction between PQ and CQ (Pukrittayakamee et al., 2014) and also between PQ and PIP (Hanboonkunuprakarn et al., 2014). It is uncertain whether this observed drug-drug interaction would result in clinically significant increase or decrease in the transmission blocking, radical curative, or toxic effects of PQ.

## CONCLUSION

The pharmacokinetic studies conducted in Thai population during the years 1980-2017 have provided information that are useful for optimization of dosage regimens of both CQ and PQ for the treatment of malaria. In general, the impacts of ethnic difference, malaria infection and/or G6PD status are minimal and should not significantly influence the pharmacokinetics of both drugs and thus, treatment outcomes. Clinical efficacy of both drugs for treatment of malaria, either as blood schizonticide, tissue schizonticide or gametocytocide remains at satisfactory level. Although results from some studies provide evidence for the possibility of pharmacokinetic drug interactions of PQ and other co-administered antimalarial drugs, clinical relevant

pharmacokinetic drug interactions when PQ is co-administered with other antimalarial drugs in patients with malaria, is still an issue of further investigations. The major limitations of the clinical application of the information for dose optimization of both drugs in malaria patients are wide variability in pharmacokinetics (particularly CQ) among individuals including inconsistent analysis procedures (sensitivity of the analytical methods for measurement of drug concentrations and approaches in pharmacokinetic data analysis). Furthermore, there has been small number of studies relating to clinical pharmacokinetics of both drugs in Thai population. Information of the clinical pharmacokinetics of both drugs in vulnerable groups of patients (that is, pregnant women, children, patients with concomitant renal and/or hepatic impairments) has been limited. Further studies of clinical pharmacokinetics of CQ and PQ in such groups of patients are essential for dose optimization in malaria treatment, particularly in the current situation of drug resistant malaria.

## CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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