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Effects of Plasmodium falciparum infection on the pharmacokinetics of quinine and its metabolites in pregnant and non pregnant Sudanese women

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3 **Effects of *Plasmodium falciparum* infection on the pharmacokinetics of**
4 **quinine and its metabolites in pregnant and non pregnant Sudanese**
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6 **women**
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Abstract

Purpose

The study aimed to investigate the effects of *plasmodium falciparum* infection on the pharmacokinetics of quinine and its metabolites in pregnant and non pregnant Sudanese women.

Methods

In a case-control study, nine pregnant & eight non-pregnant Sudanese women infected with *P. falciparum* were treated with intramuscular artemether. Before given artemether they received a single dose of quinine hydrochloride as intravenous infusion. Blood samples were collected frequently and analysed for quinine and its metabolites (phase I). One week later (after clearance of parasitaemia) the quinine part of the protocol was repeated (phase II).

Results

During phase I, the mean \pm SD AUC of quinine and its major metabolite, 3-hydroxyquinine, in pregnant women was 428.2 ± 132.4 and 27.8 ± 14.1 $\mu\text{mol.l}^{-1}\text{.h}$, respectively. In non pregnant women the mean \pm SD AUC of quinine and 3-hydroxyquinine, was 517.8 ± 100.0 and 32.3 ± 15.3 $\mu\text{mol.l}^{-1}\text{.h}$. In pregnant women the mean (90% confidence intervals) AUC ratio of phase I/phase II of quinine and 3-hydroxyquinine was 1.6 (0.61, 4.22) and 1.01 (0.18, 5.60). In non pregnant the mean (90% confidence intervals) AUC ratio of phase I/phase II of quinine and 3-hydroxyquinine, was 1.93 (1.74, 2.15) and 1.19 (0.95, 1.47).

Conclusions

Plasmodium falciparum infection significantly increases plasma concentration of quinine in non pregnant women and showed the same trend in pregnant women.

1. Introduction

Malaria is a major global health problem and especially in sub-Saharan Africa. Pregnant women and children under the age of five are in particular vulnerable to the disease. In endemic areas, pregnant women are highly susceptible to malaria with both higher frequency and severity than other groups. Many complications are associated with *Plasmodium falciparum* malaria infection during pregnancy such as low birth weight, stillbirth, maternal anaemia and mortality [1]

Quinine is an important drug for the treatment of severe or multi-drug-resistant *P. falciparum* malaria [2]. Quinine is eliminated mainly by metabolism with no more than 13% of the absorbed drug excreted unchanged in urine [3]. The pharmacokinetics of quinine are reported to be altered during malaria and this alteration is in proportion to the severity of the infection. A marked increase in the area under the plasma concentration versus time curve (AUC) and volume of distribution was reported earlier. Pukrittayakamee et al have reported the reduction of total quinine clearance from $3.4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ during convalescence to $1.4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ during infection [4-6].

Therapeutic treatment doses with quinine are safe during pregnancy [7-10]. Quinine efficacy in pregnant women was reported to be poor [11]. This may be caused by the physiological changes which are associated with pregnancy. The combination of the malaria infection with pregnancy may affect the metabolism and pharmacokinetics of drugs. However, there is a lack of detailed studies that compare the pharmacokinetics of quinine and its metabolites during infection to that at recovery in pregnant and non pregnant women.

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3 In this study, we investigated the pharmacokinetics of quinine and its
4 metabolites in pregnant and non-pregnant Sudanese control group of women
5 during acute *P. falciparum* malaria infection and after treatment.
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2. Methods

2.1. Ethics

An informed consent was obtained from women who participated in the study after being given adequate information on the objectives and benefits of the project. The study was monitored and supervised by qualified medical personnel whose first responsibility was the welfare of the patients enrolled in the study. At all times, proper patient management took priority over continuation of the study. The study was carried out following WHO Guidelines for good clinical practice. The ethical committee of the University of Khartoum's Faculty of Medicine and the Human Ethics committee at the Federal Ministry of Health, Khartoum, Sudan approved the study protocol.

2.2. Study design and subjects

It was a case-control study in which nine pregnant and eight non-pregnant Sudanese women in their second or third trimester infected with *P. falciparum* were asked to participate. The patients received a single dose of (10mg/kg body weight) quinine hydrochloride (lab. Renaudin, Saint Cloud, France) as intravenous infusion during 2 hours. Twelve hours later they received the first dose of artemether (methyl ether of dihydroartemisinin, Kunming Pharmaceutical Corp. Qigongli, West Suburb, Kunming, China) 1.6mg/kg body weight, intramuscularly. The second dose of artemether was given eight hours after the first dose. Thereafter they were given one dose daily for four days. All drug administrations were supervised by our staff.

Blood samples were collected before quinine administration and at 0.5, 1, 2, 4, 12, 24, 48 and 72 hours thereafter (phase I). One week later after the initial dose administration at phase I, the quinine part of the protocol was repeated

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4 (phase II) in order to compare the pharmacokinetics of quinine and its
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6 metabolites during infection and after treatment. Blood samples were
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8 centrifuged at 2500 rpm, plasma was separated and kept at -20°C until
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10 analysis.

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12 Duplicate samples of plasma were analysed for quinine and its metabolites 3-
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14 hydroxyquinine (3-OHQ), (10R)-10,11-dihydroxyquinine ((10R)-DOHQ) and
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16 (10S)-10,11-dihydroxyquinine ((10S)-DOHQ) using high performance liquid
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18 chromatography (HPLC) as described [12]. The lower limit of quantitation of
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20 quinine and its metabolites was 5 nM. Three different concentration ranges of
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22 the calibration curves were used. For each calibration curve a blank plasma
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24 sample and four to five calibration points were used. The within and between
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26 assay coefficient of variations of the method were less than 15% for all the
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28 analytes.
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34 **Parasitological and clinical data:**

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36 For diagnosis of malaria infection and during follow up after treatment, blood
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38 was obtained by a finger prick.
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41 Thick and thin blood films were prepared and stained with Giemsa (Ph 7.0,
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43 diluted with phosphate buffered saline). The thick blood films were used to
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45 detect the malaria parasite and the thin films for defining the parasite species.
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49 For parasite detection, 100 fields were examined irrespective of the parasites
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51 encountered. Parasitological data were cross-checked by another technician,
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53 blinded to the results and verified by the senior technologist if there was any
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55 controversy. The number of asexual parasites per 200 leukocytes was
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57 counted and parasite density (asexual parasites/ μ l) was calculated assuming
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59 a normal value of 6000 leukocytes/ μ l.
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3 All women enrolled in this study were those who presented with mild and
4 uncomplicated *P. falciparum* malaria, those who presented with mixed
5 infections or with severe malaria as defined by the WHO criteria for severe
6 disease [13] were excluded.
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12 All the subjects were followed very closely. Body temperature was recorded
13 every 6 hr until it decreased to 37.5 C and remained stable for the next 48 hr,
14 then daily. Blood parasite counts were estimated every 6 hr until cleared, then
15 daily. Radical cure was defined as the absence of asexual parasites during
16 the 28-day follow-up. Parasite clearance time (PCT) was the time from the
17 initiation of treatment until the first time a slide was negative for the asexual
18 parasite forms, and remained negative for the next 24 hr. Fever clearance
19 time (FCT) was defined as the time from the start of treatment until the body
20 temperature subsided to 37.5 °C and remained at or below this temperature
21 for the next 48 hr.
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39 **2. 3. Pharmacokinetic calculations**

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41 The pharmacokinetic parameters were determined using non-compartmental
42 methods. The total area under the plasma concentration time curve (AUC) of
43 quinine and its metabolites was determined as $AUC_{0-72} + AUC_{72-\infty}$. AUC_{0-72}
44 was estimated by the linear trapezoidal rule and $AUC_{72-\infty}$ was calculated as
45 c/k where c is the last time concentration point and k is the elimination rate
46 constant estimated by linear regression of the 3 to 6 last points of the plasma
47 concentration time curve. The maximum plasma concentrations (C_{max}) and
48 (t_{max}) time to attain C_{max} were estimated from observed plasma concentration
49 versus time data. The elimination half-life $t_{1/2}$ was determined as $0.693/k$.
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2. 4. Statistical analysis

We used \log_e - transformed data and determined geometric means of the pharmacokinetic parameters for quinine, 3-hydroxyquinine, (10R)-10,11dihydroxyquinine and (10S)-10,11dihydroxyquinine in phase I and phase II, respectively with 95% confidence intervals (CIs) from the untransformed data separate for pregnant and non-pregnant (control group) women. Intraindividual ratios of geometric means of phase I to phase II for the pharmacokinetic parameters with corresponding 90% CIs were calculated. Mann-Whitney U test was used to check for differences in $t_{1/2}$ and t_{\max} between phase I and phase II for pregnant and non pregnant women.

3. Results

Quinine was detected in the sample of one of the pregnant patients before drug administration and thus this subject was excluded from the study.

All the patients completed the study except for two of the controls that quitted the second part of the study. The treatment was generally well tolerated and only tinnitus was reported by a minor number of patients. All participants recovered uneventfully from their *P. falciparum* infection.

The ages and weights of the pregnant women were (mean±SD) 26.6± 8.5 years and 55.7±14.9 kg, respectively. The ages and weights of the control group were (mean±SD) 25.2±7.9 years and 52.3±12.7 kg, respectively.

The mean parasite clearance time (PCT) was 51.2 +/- 23.2 hours while the fever clearance time (FCT) was 38.0 +/- 31.3 hours. All *P. falciparum* infected women cleared parasites and were free of fever by the end of day 3 except for one pregnant women (primigravidae) who had a parasite clearance time by day 4 following initiation of treatment. None of the study subjects had parasites in blood or fever before the start of phase II of the study or on day 14, 21 and 28.

The plasma concentration profiles of quinine, 3-hydroxyquinine, (10R)-10,11-dihydroxyquinine and (10S)-10,11-dihydroxyquinine for pregnant and non pregnant women during phase I and II are shown in figures 1A-1D, respectively.

Pharmacokinetic parameters of quinine, 3-hydroxyquinine, (10R)-10,11-dihydroxyquinine and (10S)-10,11-dihydroxyquinine in pregnant and non pregnant women during phase I and phase II are shown in Table 1 and 2.

In pregnant women, there were no statistically significant changes in the pharmacokinetic parameters of quinine and its metabolites between phase I and II of the study as presented by the ratios of geometric means and 90% confidence intervals shown in Table I. However,

1 during phase I the geometric mean AUC and C_{\max} of quinine were higher by 60 and 55 %,
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4 respectively.

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6 Only slight mean changes were observed in the AUC and C_{\max} of the other two metabolites,
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8 and no remarkable differences were found in the $t_{1/2}$ or t_{\max} of quinine and its metabolites.

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11 As shown in Table II for the control group, there was a significant decrease in the geometric
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13 mean AUC and C_{\max} of quinine which is reflected by the geometric mean ratio of phase I to
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15 phase II (1.93, 90 % CI 1.74, 2.15) and (1.35, 90 % CI 1.21, 1.50), respectively. However,
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17 no significant changes were observed in $t_{1/2}$ ($p=0.89$) and t_{\max} ($p=0.78$) of quinine.
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19 Furthermore, we observed no significant changes in the pharmacokinetic parameters (AUC,
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23 C_{\max} , $t_{1/2}$ and t_{\max}) for the three metabolites of quinine.
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4. Discussion:

In this study we compared the pharmacokinetics of quinine and three of its metabolites during infection to their pharmacokinetics at recovery. This was done in pregnant and non-pregnant (control) women. Quinine pharmacokinetics have been reported to be changed by a number of factors such as co-administration of inhibitors [14] or inducers [15] of CYP3A4, cigarette smoking [16] and *Plasmodium falciparum* infection [17].

The pharmacokinetics of medications taken during pregnancy can be modified due to physiological changes such as alterations in gastrointestinal transit time, increased glomerular filtration rate [18] and increased total body water and fat. Furthermore, levels of sex hormones change significantly during pregnancy [19] and that in turn may affect the activity of the different cytochrome P450 enzymes [20-23], which are involved in the metabolism of endogenous compounds and drugs. In general, changes in pharmacokinetics of drugs during pregnancy are well documented [24]. Specifically, these changes may alter exposure to quinine, which could compromise its efficacy or increase concentration dependent side effects.

Cytochrome P450 3A4 is the major drug metabolising enzyme [25], which catalyses the biotransformation of quinine to 3-hydroxyquinine. A known marker for induction of hepatic cytochrome P450 3A4 is 6 β -hydroxycortisol formation [26-29]. Using this marker studies performed in pregnant women have shown a significant increase in the formation of this metabolite during pregnancy in comparison to postpartum [30] indicating higher activity of CYP3A.

The statistically significant increase in the AUC and C_{max} of quinine during infection that we found in the control group is consistent with what was reported in literature [31]. Quinine is known to bind to α -acid glycoprotein which is an acute phase reactant that significantly increases during malaria infection [32]. This explains the increased levels of quinine during infection. Even though the elevation of quinine AUC and C_{max} in pregnant

1 women was not statistically significant, it was in agreement with the results found in the
2 control group. This may be explained by the greater inter-individual variability in the
3 pregnant women group. The lack of significant changes in the AUC and C_{max} of the
4 metabolites indicates that the malaria infection has no pronounced effect on the drug
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14 Furthermore, the degree of protein binding and excretion of the metabolites may be different
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as well be possible explanations of the lack of significant differences in the
pharmacokinetics of the metabolites.

In conclusion, our results indicate that plasmodium *falciparum* infection has more
profound effect on the plasma concentration of quinine than on the plasma concentration of
quinine metabolites when a single dose of quinine is administered. However, steady state
pharmacokinetic parameters of the drug and its metabolites have to be studied in order to
determine whether quinine dose adjustment is needed during infection with *p. falciparum*.

Conflicts of interest statement

The authors have no conflict of interest concerning the work reported in this paper.

Table I. Pharmacokinetic parameters of quinine, 3-hydroxyquinine, (10R)-10,11dihydroxyquinine and (10S)-10,11dihydroxyquinine when a single 10mg/kg dose of quinine hydrochloride was given to 9 pregnant women during phase I and II of the study. Results are shown as Geometric Means (95% CI) and Ratios (phase I / phase II) of Geometric Means with (90% CI). T_{max} and $t_{1/2}$ are presented as median (range)

	C_{max} ($\mu\text{mol/l}$)	t_{max} (h)	$t_{1/2}$ (h)	AUC ($\mu\text{mol.l}^{-1}.\text{h}$)
Quinine				
Geometric Mean in phase I (95% CI)	30.92 (19.38, 49.32)	2.0 (1.0 - 4.0)	12.5 (6.2 – 15.7)	455.94 (368.22, 564.54)
Geometric Mean in phase II (95% CI)	19.99 (16.59, 24.08)	2 (2.0 – 4.0)	12.8 (8.6 – 16.6)	284.90 (222.00, 365.61)
Ratios of Geometric Means (90% CI)	1.54 (0.35, 6.79)			1.6 (0.61, 4.22)
3-hydroxyquinine				
Geometric Mean in phase I (95% CI)	0.86 (0.53, 1.38)	12.0 (4.6 – 12.0)	17.3 (9.4 – 18.6)	25.93 (16.28, 41.30)
Geometric Mean in phase II (95% CI)	0.96 (0.63, 1.48)	4.0 (4.0 – 12.0)	14.9 (9.4 – 22.4)	25.74 (18.21, 36.39)
Ratios of Geometric Means (90% CI)	0.90 (0.13, 5.96)			1.01 (0.18, 5.60)
(10R)-10,11dihydroxyquinine				
Geometric Mean in phase I (95% CI)	0.37 (0.24, 0.55)	4.0 (4.0 – 4.0)	9.6 (5.5 – 12.9)	6.22 (4.16, 9.30)
Geometric Mean in phase II (95% CI)	0.30 (0.20, 0.45)	4 (2.0 – 4.0)	9.9 (6.3 – 13.3)	4.49 (2.99, 6.75)
Ratios of Geometric Means (90% CI)	1.22 (0.22, 6.85)			1.39 (0.26, 7.54)
(10S)-10,11dihydroxyquinine				
Geometric Mean in phase I (95% CI)	0.31 (0.23, 0.42)	4.0 (4.0 – 12.0)	9.8 (6.7 – 14.1)	5.36 (3.95, 7.27)
Geometric Mean in phase II (95% CI)	0.38 (0.29, 0.50)	4.0 (2.0 – 4.0)	9.4 (6.6 – 15.6)	5.39 (3.97, 7.32)
Ratios of Geometric Means (90% CI)	0.83 (0.25, 2.79)			1.0 (0.28, 3.58)

Table II. Pharmacokinetic parameters of quinine, 3-hydroxyquinine, (10R)-10,11 dihydroxyquinine and (10S)-10,11dihydroxyquinine when a single 10mg/kg dose of quinine hydrochloride was given to 8 non pregnant women (controls) during phase I and 6 non pregnant women during phase II of the study. Results are shown as Geometric Means (95% CI) and Ratios (phase I / phase II) of Geometric Means with (90% CI). T_{max} and $t_{1/2}$ are presented as median (range)

	C_{max} ($\mu\text{mol/l}$)	t_{max} (h)	$t_{1/2}$ (h)	AUC ($\mu\text{mol.l}^{-1}.\text{h}$)
Quinine				
Geometric Mean in phase I	26.73	2.0	11.4	504.18
(95% CI)	(21.45, 33.31)	(2.0 – 4.0)	(6.7 – 13.8)	(411.05, 618.42)
Geometric Mean in phase II	19.91	2.0	10.9	260.60
(95% CI)	(15.01, 26.41)	(2.0 – 4.0)	(8.9 – 15.1)	(192.04, 353.63)
Ratios of Geometric Means	1.35			1.93
(90% CI)	(1.21, 1.50)			(1.74, 2.15)
3-hydroxyquinine				
Geometric Mean in phase I	0.91	4.0	13.1	28.40
(95% CI)	(0.59, 1.40)	(4.0 – 15.0)	(6.2 – 19.0)	(17.45,46.24)
Geometric Mean in phase II	1.07	4	13.4	23.96
(95% CI)	(0.69, 1.66)	(4.0 – 12.0)	(9.6 – 23.1)	(14.75,38.92)
Ratios of Geometric Means	0.85			1.19
(90% CI)	(0.70, 1.02)			(0.95, 1.47)
(10R)-10,11dihydroxyquinine				
Geometric Mean in phase I	0.28	4.0	12.1	7.04
(95% CI)	(0.15, 0.53)	(2.0 – 6.0)	(6.4 – 28.0)	(3.36,14.76)
Geometric Mean in phase II	0.40	4.0	10.2	6.69
(95% CI)	(0.20, 0.79)	(2.0 – 4.0)	(4.8 – 11.9)	(3.66,12.22)
Ratios of Geometric Means	0.71			1.05
(90% CI)	(0.53, 0.95)			(0.77, 1.60)

(10S)-10,11dihydroxyquinine				
Geometric Mean in phase I (95% CI)	0.31 (0.17, 0.55)	4.0 (4.0 – 6.0)	11.5 (6.1 – 22.0)	6.47 (3.64,11.51)
Geometric Mean in phase II (95% CI)	0.35 (0.17, 0.75)	4.0 (2.0 – 4.0)	10.1 (7.4 – 12.3)	5.54 (2.61,11.76)
Ratios of Geometric Means (90% CI)	0.87 (0.65, 1.16)			1.17 (0.88, 1.56)

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Fig. 1A

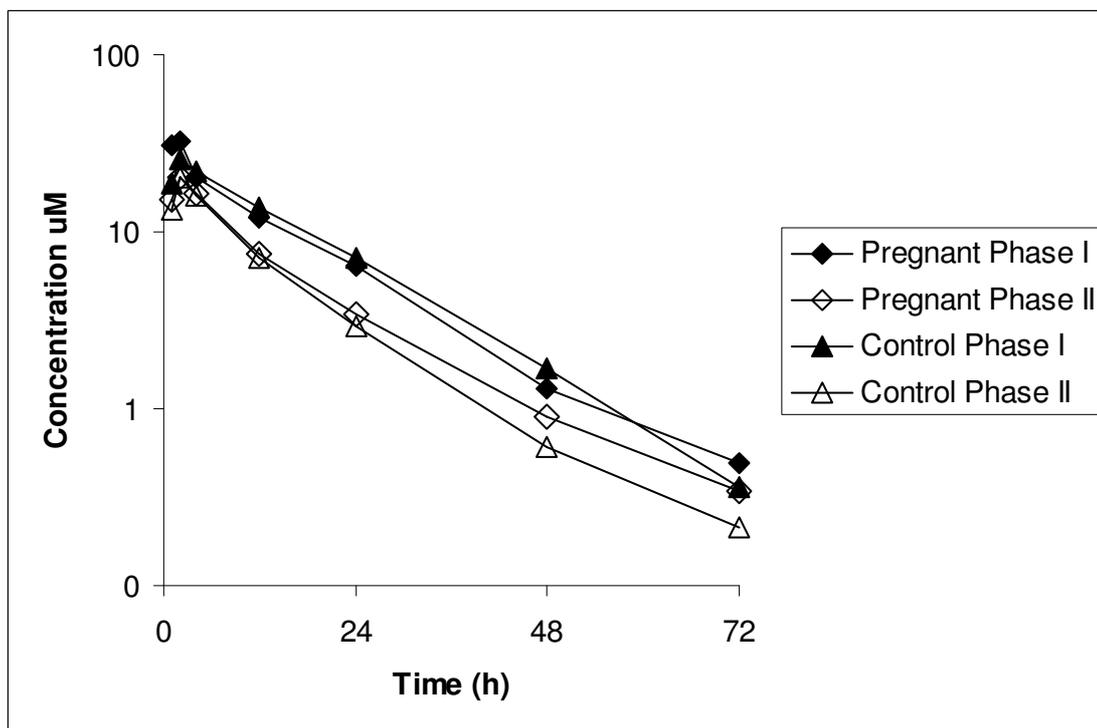


Fig. 1B

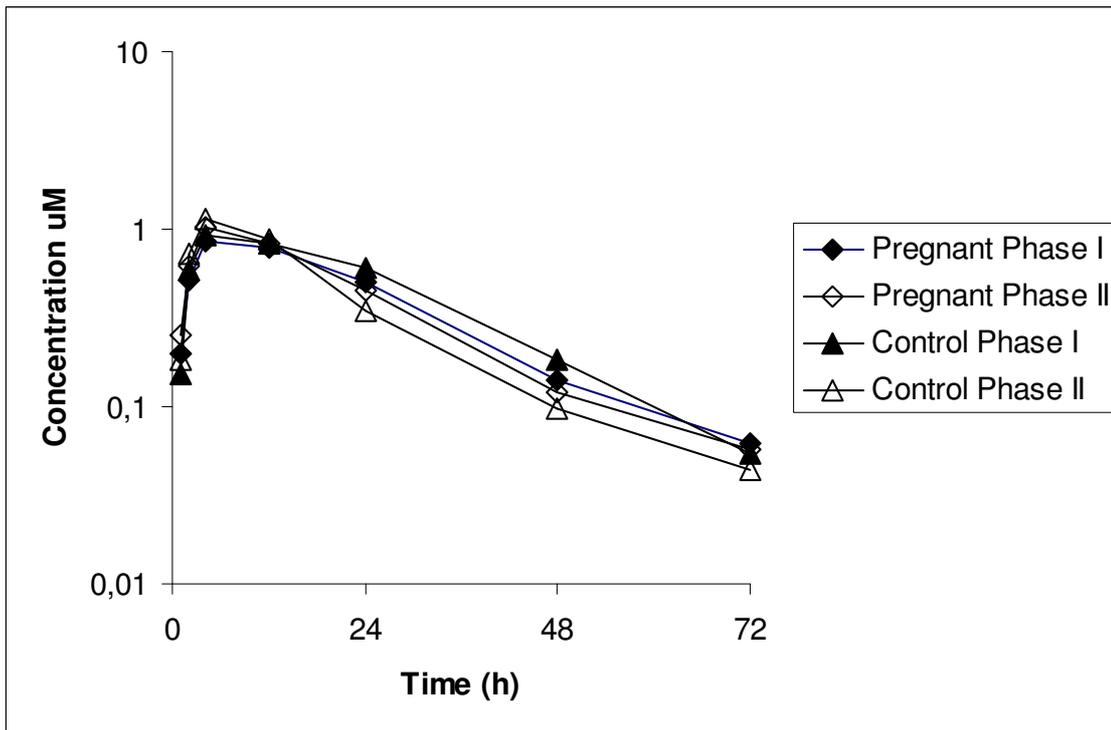


Fig 1C

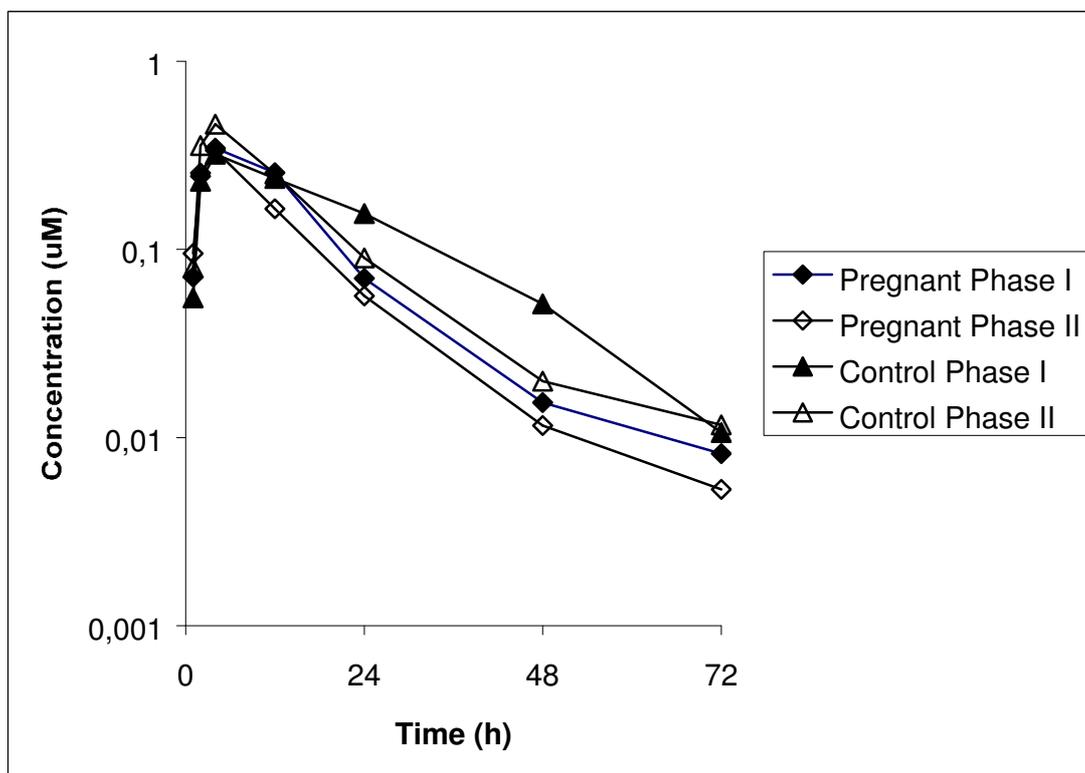


Fig 1D

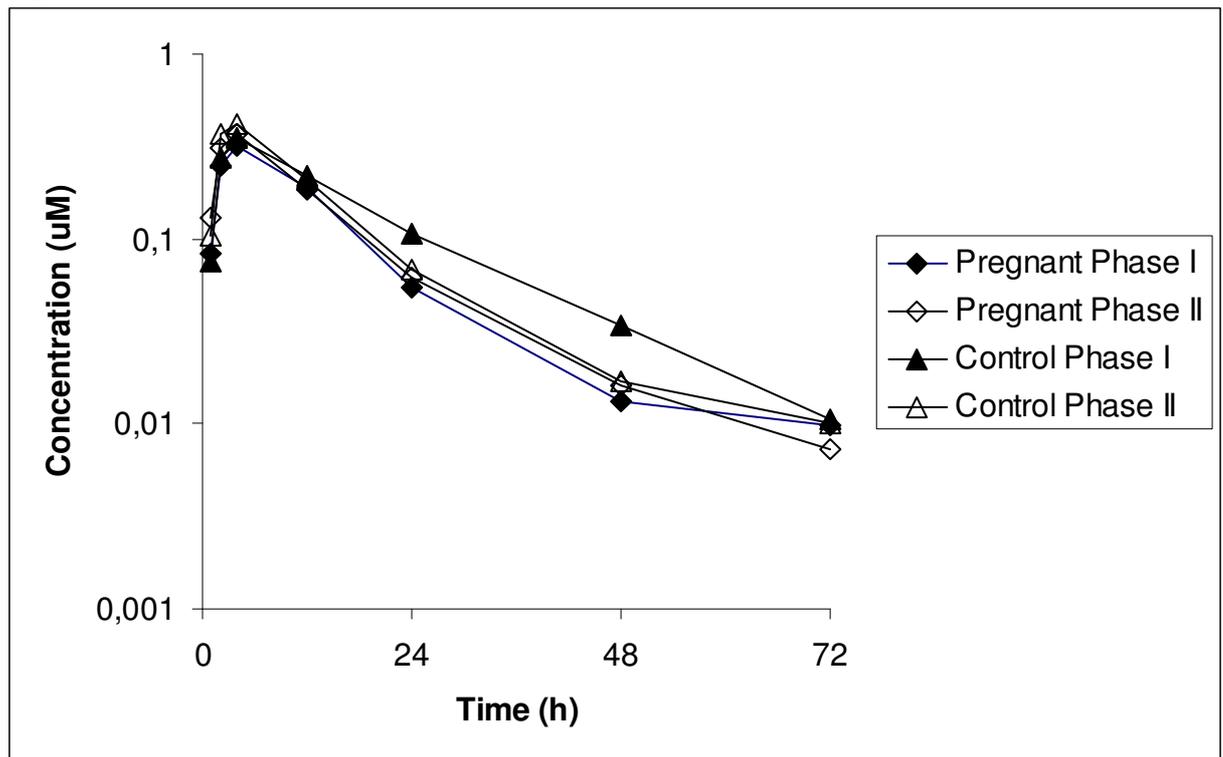


Figure legend

Fig 1: Mean plasma concentration-time profiles in pregnant women and controls infected with *Plasmodium falciparum* after infusion of a single dose (2 hours) of quinine hydrochloride (10mg/kg body weight), during phase I (infection) and II (infection free).

A, quinine; B, 3-hydroxyquinine; C, (10S)-10,11-dihydroxyquinine; D, (10R)-10,11-dihydroxyquinine.

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References

1. Shulman, C.E., Dorman, E.K., 2003. Importance and prevention of malaria in pregnancy." *Trans. R. Soc. Trop. Med. Hyg.* 97, 30-35.
2. White, N.J., 1996. The treatment of malaria. *N. Engl. J. Med.* 335, 800-806.
3. Mirghani, R. A., Hellgren, U., et al., 2003. Metabolism and elimination of quinine in healthy volunteers." *Eur J Clin Pharmacol.* 59, 423-427.
4. White NJ, Looareesuwan S, Warrell DA, Warrell MJ, Bunnag, D, Harinasuta T 1982. Quinine pharmacokinetics and toxicity in cerebral and uncomplicated falciparum malaria. *Am J Med* 73: 564±572
5. Pukrittayakamee, S., S. Looareesuwan, D. Keeratithakul, T. M. E. Davis, P. Teja-Isavadharm, B. Nagachinta, A. Weber, A. L. Smith, D. Kyle, and N. J. White. A study of the factors affecting the metabolic clearance of quinine in malaria. *Eur. J. Clin. Pharmacol* 1997; 52:487-493.
6. White, N. J. Assessment of the pharmacodynamic properties of antimalarial drugs in vivo. *Antimicrob. Agents Chemother* 1997. 41:1413-1422
7. Looareesuwan, S., Phillips, R.E., et al., 1985. Quinine and severe falciparum malaria in late pregnancy. *Lancet* 2, 4-8.
8. Looareesuwan, S., White, N.J., et al., 1987. Quinine and severe falciparum malaria in late pregnancy. *Acta Leiden* 55, 115-120.
9. McGready, R., Cho, T., et al., 1998. Quinine and mefloquine in the treatment of multidrug-resistant *Plasmodium falciparum* malaria in pregnancy. *Ann. Trop. Med. Parasitol.* 92, 643-653.

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10. Phillips-Howard, P.A., Wood, D., 1996. The safety of antimalarial drugs in pregnancy. *Drug Saf.* 14, 131-145.
 11. McGready R, Ashley EA, Moo E, Cho T, Barends M, Hutagalung R, et al 2005. A randomized comparison of artesunate-atovaquone-proguanil versus quinine in treatment for uncomplicated falciparum malaria during pregnancy. *J Infect Dis*;192, 846-53
 12. Mirghani, R. A., Ericsson, O., et al., 2001. Simultaneous determination of quinine and four metabolites in plasma and urine by high-performance liquid chromatography. *J. Chromatogr. B. Biomed. Sci. Appl.* 754, 57-64.
 13. World Health Organization. Severe falciparum malaria. *Trans R Soc Trop Med Hyg.* 2000; 94(suppl 1):S1–S90
 14. Mirghani RA, Hellgren U, Westerberg PA, Ericsson O, Bertilsson L, Gustafsson LL 1999. The roles of cytochrome P450 3A4 and 1A2 in the 3-hydroxylation of quinine in vivo. *Clin Pharmacol Ther* 66:454–460.
 15. Wanwimolruk S, Kang W, Coville PF, Viriyayudhakorn S, Thitiarchakul S 1995 Marked enhancement by rifampicin and lack of effect of isoniazid on the elimination of quinine in man. *Br J Clin Pharmacol* 40:87–91
 16. Pukrittayakamee S, Pitisuttithum P, Zhang H, Jantra A, Wanwimolruk S, White NJ. 2002. Effects of cigarette smoking on quinine pharmacokinetics in malaria. *Eur J Clin Pharmacol.* 58(5):315-

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59
60
17. Babalola CP, Bolaji OO, Ogunbona FA, Sowunmi A, Walker O. Pharmacokinetics of quinine in African patients with acute falciparum malaria 1998. *Pharm World Sci.* 20(3):118-22.
 18. Hladunewich, M.A., Lafayette, R.A., et al., 2004. The dynamics of glomerular filtration in the puerperium." *Am. J. Physiol. Renal Physiol.* 286, 496-503.
 19. Xu B Pekkanen, J., et al. 2003. Maternal sex hormones in early pregnancy and asthma among offspring: a case-control study. *J. J. Allergy Clin. Immunol.* 112, 1101-104.
 20. Laine, K., Tybring, G., et al., 2000. No sex-related differences but significant inhibition by oral contraceptives of CYP2C19 activity as measured by the probe drugs mephenytoin and omeprazole in healthy Swedish white subjects." *Clin. Pharmacol. Ther.* 68, 151-159.
 21. Laine, K., Yasar, U., et al., 2003. A screening study on the liability of eight different female sex steroids to inhibit CYP2C9, 2C19 and 3A4 activities in human liver microsomes. *Pharmacol. Toxicol.* 93, 77-81.
 22. Palovaara, S., Pelkonen, O., et al., 2003. Inhibition of cytochrome P450 2B6 activity by hormone replacement therapy and oral contraceptive as measured by bupropion hydroxylation. *Clin. Pharmacol. Ther.* 74, 326-333.
 23. Palovaara, S., Tybring, G., et al., 2003. The effect of ethinyloestradiol and levonorgestrel on the CYP2C19-mediated metabolism of omeprazole in healthy female subjects. *Br. J. Clin. Pharmacol.* 56, 232-237.

- 1
2
3
4 24. Loebstein, R., Lalkin, A., et al., 1997. Pharmacokinetic changes during
5 pregnancy and their clinical relevance. *Clin. Pharmacokinet.* 33, 328-
6 343.
7
8
9
10 25. Shimada, T., Yamazaki, H., et al., 1994. Interindividual variations in
11 human liver cytochrome P-450 enzymes involved in the oxidation of
12 drugs, carcinogens and toxic chemicals: studies with liver microsomes
13 of 30 Japanese and 30 Caucasians. *J. Pharmacol. Exp. Ther.* 270,
14 414-423.
15
16
17 26. Kovacs, S. J., Martin, D.E., et al., 1998. Urinary excretion of 6 beta-
18 hydroxycortisol as an in vivo marker for CYP3A induction: applications
19 and recommendations. *Clin. Pharmacol. Ther.* 63, 617-622.
20
21
22 27. Totsuka, S., Watanabe, T., et al. 1999. "Increase in urinary excretion of
23 6beta-hydroxycortisol in common marmosets as a marker of hepatic
24 CYP3A induction." *Arch Toxicol* 73(4-5): 203-207.
25
26
27 28. Eeckhoudt, S.L., Desager, J.P., et al., 2001. Midazolam and cortisol
28 metabolism before and after CYP3A induction in humans. *Int. J. Clin.*
29 *Pharmacol. Ther.* 39, 293-299.
30
31
32 29. Galteau, M.M., Shamsa, F., 2003. Urinary 6beta-hydroxycortisol: a
33 validated test for evaluating drug induction or drug inhibition mediated
34 through CYP3A in humans and in animals. *Eur. J. Clin. Pharmacol.* 59,
35 713-733.
36
37
38 30. Ohkita, C., Goto, M., 1990. Increased 6-hydroxycortisol excretion in
39 pregnant women: implication of drug-metabolizing enzyme induction."
40 *DICP* 24, 814-416.
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59
60
31. Silamut, K., White, N.J., et al., 1985. Binding of quinine to plasma proteins in falciparum malaria." *Am. J. Trop. Med. Hyg.* 34, 681-686.
32. Wanwimolruk, S., Denton, J.R., 1992. Plasma protein binding of quinine: binding to human serum albumin, alpha 1-acid glycoprotein and plasma from patients with malaria. *J. Pharm. Pharmacol.* 44, 806-811.

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