PHARMACOKINETICS OF MEFLOQUINE WITH DIHYDROARTEMISININ AS 2-DAY REGIMENS IN PATIENTS WITH UNCOMPLICATED FALCIPARUM MALARIA

Le Thi Diem Thuy[1,2], Le Ngoc Hung[1], Nguyen Canh Hung[3] and Kesara Na-Bangchang[2]

[1]Pharmacology and Toxicology Unit, Graduate Program in Biomedical Sciences, Faculty of Allied Health Sciences, Thammasat University, Pathum Thani, Thailand; [2]Cho Ray Hospital, Ho Chi Minh City, Vietnam; [3]Lam Dong II Hospital, Lam Dong, Vietnam

Abstract. The objective of this study was to investigate the pharmacokinetics of mefloquine (MQ) when given as 750 mg at two different times in combination regimens with dihydroartemisinin (DHA) in patients with acute uncomplicated falciparum malaria. A total of 12 Vietnamese patients (6 in each group) were randomized to receive two MQ-DHA regimens as follows: regimen-A: an initial oral dose of 300 mg DHA, followed by 750 mg MQ and 300 DHA 6 and 24 hours later; regimen-B: an initial dose of 300 mg DHA, followed by 300 mg DHA and 750 mg MQ at 24 hours. Both combination regimens were well tolerated. All patients responded well to treatment with no recrudescence during a 42 day follow-up period. The pharmacokinetics of MQ following both regimens were similar but pooled data from both groups suggest that the kinetics of MQ was different from that observed in Vietnamese healthy subjects reported in a previous study. The median (95% CI) time period for maintenance of whole blood MQ concentrations above 500 ng/ml was 16 (0-24) days. It was concluded that since no pharmacokinetic drug interaction was observed, MQ dose given 24 hours after an initial dose of DHA is a preferable combination treatment regimen with regard to patient compliance.

INTRODUCTION

Mefloquine (MQ) is considered a main counterpart to artemisinin derivatives in combination regimens. In these combination regimens, MQ has been used at different dosages, *ie,* 10 mg/kg (Hung *et al*, 1997), 15 mg/kg (Na-Bangchang *et al,* 1999) and 25 mg/kg (Looareesuwan *et al,* 1994), given initially, or at 2, 6, 8, or 24 hours or at 4 days after the first dose of artemisinin derivative (Looareesuwan *et al*, 1994; Hung *et al*, 1997; Na-Bangchang *et al*, 1999; Simpson *et al*, 1999; Wang *et al*, 2001; Hung *et al*, 2004). The treatment duration of the combination regimens also varies from a single combined dose to a 4 day-combination regimen (Na-Bangchang *et al*, 1999; Simpson *et al*, 1999; Hung *et al*, 2004). One of the reasons for having such different combination regimens is the limitation of information on drug interactions between artemisinin derivatives and MQ. The maximum concentration (C_{max}) and the area under the concentration-time curve (AUC) of MQ given at 24 hours after oral dihydroartemisnin (DHA) was lower than that when MQ was given alone in malaria patients (Hung *et al*, 1999). These findings were also observed when MQ was given after artesunate or artemether (Karbwang *et al*, 1994; Na-Bangchang *et al,* 1995). However, no significant change in pharmacokinetics of MQ was observed when given concurrently with DHA in Thai healthy subjects, except for

Correspondence: Professor Kesara Na-Bangchang, Graduate Program in Biomedical Sciences, Faculty of Allied Health Sciences, Thammasat University (Rangsit Campus), Pathum Thani 12121, Thailand. E-mail: kesaratmu@yahoo.com

a delay in drug absorption (Na-Bangchang *et al*, 1999). The clearance and volume of distribution of MQ are often reduced in parallel with the severity of the malaria illness (White *et al*, 1982). Furthermore, drug interaction, together with a high inter-individual variability can markedly influence the kinetics of MQ. More studies on pharmacokinetics of MQ in the combination regimens with artemisinin derivatives are needed to explore the possibility of drug interaction between the two drugs as well as to optimize therapy with these combination regimens. We have conducted a pharmacokinetic study of MQ given in two different regimens, *ie*, at 6 hours after the first dose of DHA, and at 24 hours concurrently with the second dose of DHA, in Vietnamese patients with acute uncomplicated falciparum malaria.

PATIENTS AND METHODS

Patients

The study was carried out at Lam Dong II Hospital, Bao Loc District, Lam Dong Province in the southern part of Vietnam from October 2002 to August 2003. The study was approved by the Ethics Committee of Cho Ray Hospital, Ho Chi Minh City, Vietnam. Twelve male patients with acute uncomplicated *Plasmodium falciparum* malaria were included in the study. The inclusion criteria included: age 16-60 years, signs/symptoms of acute uncomplicated falciparum malaria with asexual parasitemia between 1,000 and 200,000 /μl (0.2-4% infected red blood cells), no history of liver or kidney diseases, and written informed consent given for study participation. The exclusion criteria included: mixed infection with *P. vivax*, signs/symptoms of severe/complicated falciparum malaria, history of allergy to the study drugs, history of intake of any artemisinin derivative or MQ within the previous 2 days or 1 month, respectively.

Treatment regimens

The eligible patients were randomized to treat with one of the two DHA-MQ combination regimens (6 cases each) as follows: regimen-A: an initial oral dose of 300 mg DHA (100 mg per capsule, Drafa Pharma Pharmaceutical Company, Belgium), followed by 750 mg MQ (Lariam®, Hoffman-La Roche, Basel, Switzerland, 250 mg per tablet) 6 hours later, and 300 mg DHA at 24 hours; regimen B: an initial dose of 300 mg DHA, followed by 300 mg DHA and 750 mg MQ at 24 hours. All drugs were given with a glass of water under supervision of investigators. Patients fasted at least 4 hours before the MQ dose and food was not allowed within 2 hours of drug administration. Any patient who vomited within 1 hour of drug administration was excluded from the trial and a new patient replaced that patient. No other concurrent drugs were used during hospitalization except paracetamol and vitamin B complex (2 tablets per day).

Clinical assessments

On the first day of drug administration (day 0), patients were interviewed regarding the duration of staying in malaria endemic areas, history of malaria disease during the past 2 years, administration of antimalarials before admission, the date of first signs/symptoms of malaria. Full clinical examinations were performed twice daily until patient recovery from malaria (negative parasitemia, clearance of fever, and no clinical signs/symptoms of malaria), and then daily until discharge. Axillary temperature was recorded every 6 hours until 4 consecutively normal temperatures, and then daily until discharge. Other vital parameters, such as blood pressure and heart rate were recorded every 12 hours until clearance of fever, then daily until discharge. Routine blood examinations (hematology and biochemistry) were done on days 0, 2 and 4. Electrocardiograms (ECGs) were recorded 12 hourly during the first 24 hours of MQ intake. In the case of abnormal rhythms, ECGs were continued until 3 consecutively normal tracings. Patients were hospitalized until recovery

from malaria, and the blood samples were collected 96 hours after drug administration for MQ levels. All patients were requested to return for follow-up on days 7, 14, 21, 28, 35 and 42. Analysis of the response to treatment was adapted from the World Health Organization (1996). Efficacy was assessed using the following parameters: (1) 42 day cure rate: the proportion of patients with clearance of asexual parasites within 7 days of initiation of trial treatment without subsequent recrudescence during 42 days of follow-up; 2) parasite clearance time (PCT): defined as time from first dose to clearance of asexual parasite forms lasting at least 48 hours; and 3) fever clearance time (FCT): time from first dose until the first time the body temperature fell below 37.5ºC and remained below 37.5ºC for at least a further 48 hours.

Safety and tolerability of combination regimens were assessed based on clinical findings and laboratory (hematology and serum biochemistry) tests within 7 days of treatment initiation, and during follow-up on days 14, 21, 28, 35 and 42, per the Common Toxicity Criteria CTC grade (Cancer Therapy Evaluation Program, 1998).

Blood sample collection

Blood samples (3 ml) for quantification of MQ concentration was collected in a heparinized plastic tube, through an indwelling heparinized catheter inserted in an antecubital vein. Samples were taken before the MQ dosage, at 1, 2, 6, 12, 18, 24, 48, 72, and 96 hours, then on days 7, 14, 21, 28, 35, and 42. Whole blood samples were stored in a -20ºC freezer at the Department of Biochemistry, Cho Ray Hospital until transported (in dry ice) to the Pharmacology and Toxicology Unit, Faculty of Allied Health Sciences, Thailand, where they were stored at -80ºC until analysis.

Determination of mefloquine concentrations

MQ concentration in whole blood samples were measured by high-performance liquid chromatography (HPLC) with ultraviolet detection according to the method of Karbwang *et al* (1989). The assay was linear over the concentration range of 100 to 3,200 ng/ml (r^2 0.9996 -1.0000). The inter-day *vs* intra-day coefficients of variation (C.V.) were 12.5, 45 and 3.4% *vs* 4, 4.8 and 2.7% for MQ concentrations of 100, 400 and 1,600 ng/ml, respectively. The corresponding values for intra- *vs* inter-day accuracy values were 5.2, 2.0 and 1.5% *vs* 9.2, 3.9 and 2.9%, respectively.

Pharmacokinetic analysis

Pharmacokinetic analysis of MQ was performed based on the model-independent approach ADAPT II, release 4.0 (d' Argenio and Schumitzky, 2003). The observed maximum concentration (C_{max}) was recorded directly from the whole blood concentration-time course data. Terminal phase elimination half-life ($t_{1/2z}$) was calculated by $0.693/\lambda_z$, where λ_z is the terminal elimination rate constant. The area under the whole blood concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$) was calculated based on the trapezoidal rule with extrapolation to infinity ($AUC_{extra} = C_j/\lambda$, where C_j is the concentration at the last sampling point). The apparent clearance per fraction of drug absorbed (CL/F) was estimated from the ratio of the dose to $AUC_{0-\infty}$. The apparent volume of distribution (V_z/F) was estimated from CL/F divided by λ_z. The concentration in one for days 28, 35 or 42 was the obligating value for the precision of λ_z; without this obligating value, the estimation of λ_z was cancelled. In order to characterize absorption kinetics, two-compartment open models with first-order input with absorption lag time and first-order output were applied. Akaike's inclusion criterion was used to best select the fitting curve. The estimated concentrations from the compartment kinetic model were used to draw the concentration-time curve of the means for MQ levels at the sampling points.

Statistical analysis

The quantitative data were presented as

median (95% CI) values. Comparison of the two independent quantitative data groups was done by the Mann-Whitney *U* test. Comparison of two dependent quantitative data was done by the Wilcoxon signed-rank test. Comparison of the proportions of the two groups were performed by the chi-square test with Yates's correction or Fisher's exact test. The significance level was set at $\alpha = 0.05$ for all tests.

RESULTS

Clinical and laboratory results

Twelve male patients, aged 19-36 years were enrolled in the study, 6 in each regimen. One patient in regimen-A was excluded on final data analysis due to a high baseline whole blood concentration of MQ (452 ng/ml). The baseline characteristics of the patients are presented in Table 1. All except one patient in regimen-B resided in malaria endemic areas for longer than 1 year. Fever (≥ 37.5ºC) was recorded for all patients on admission. Other symptoms of malaria included chills (11 cases), headaches (11 cases), and sweating (10 cases). Splenomegaly (Hackett's grade 1), hematocrit <35%, hemoglobin <10 g/dl and a white blood cell count <5,000/μl were observed in 1 *vs* 1, 1 *vs* 1, 1 *vs* 0 and 2 *vs* 2 patients in regimen-A *vs* regimen-B, respectively. There were no significant differences in clinical characteristics and laboratory findings, including initial parasitemia between the two groups.

All patients recovered well from malaria symptoms within 3 days, with median (95% CI) values for PCT and FCT of 36 (18-60) *vs* 48 (24-48) hours, and 48 (42-72) *vs* 54 (42-72) hours, respectively (regimen-A *vs* -B). None had vomiting after MQ dosing. No recrudescence cases were found in either group (Table 1). There were no significant differences in the biochemistry test results on days 2 and 4 compared with baseline. One patient in regimen-B had increased SGOT and SGPT levels on days 2 and 4 (SGOT: 974 and 251 U/l; SGPT: 307 and 294 U/l, on days 2 and 4, respectively).

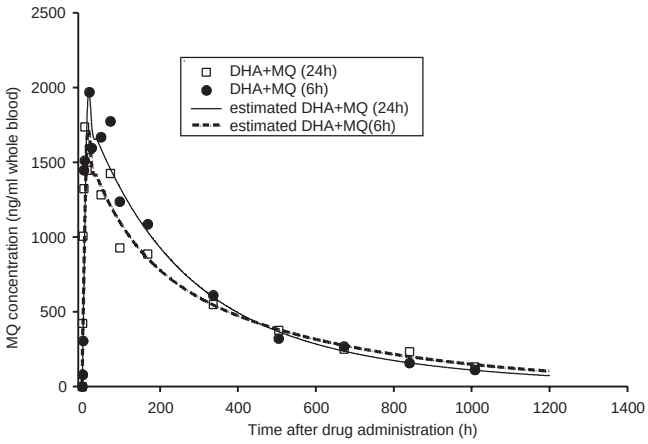

Fig 1–Median whole blood concentrations of MQ given at 6 (●: n=5) and 24 hours (□: n=6) after an oral dose of DHA in male Vietnamese patients with acute uncomplicated falciparum malaria. Concentration-time profiles were best fitted with a two-compartment open model with first-order absorption and elimination with absorption lag time.

Mefloquine pharmacokinetics

The pharmacokinetics of MQ following the two regimens were comparable (Table 2). The times for the MQ concentrations to increase above 500 ng/ml were similar between the two regimens. Pooling data from both regimens, the median (95% CI) values for C_{max}, Vd/F, CL/F, $t_{1/2z}$ and $AUC_{0-\infty}$ were 1964 (507-2,741) ng/ml, 8.9 (5.0-38.2) l/kg, 0.5 (0.4-1.5) l/day/kg, 11.0 (8.8-17.3) days, and 28,021 (9,037-33,182) ng.day/ml, respectively.

MQ concentrations higher than 500 ng/ml were associated with successful treatment outcomes. The median time to obtain a whole blood MQ concentration above 500 ng/ml was 16.25 (0-23.8) hours. There was one patient in regimen-A who had a C_{max} of 507 ng/ml and the time to reach an MQ level above 500 ng/ml was less than 1 hour.

Table 1

Demographic, baseline clinical and laboratory data on admission and treatment response in patients with acute uncomplicated falciparum malaria in regimen-A (an initial oral dose of 300 mg DHA followed by 750 mg MQ at 6 hours and 300 mg DHA at 24 hours) and regimen-B (an initial oral dose of 300 mg DHA followed by 750 mg MQ and 300 mg DHA at 24 hours. Data are presented as median (95%CI) or number (n) values.

	Regimen-A (n=5)	Regimen-B (n=6)
Clinical data on admission		
Age (yrs)	21 (19-35)	25 (19-36)
Weight (kg)	52 (45-54)	55 (53-59)
Height (cm)	161 (160-166)	165.5 (160-169)
Body temperatute (ºC)	40.0 (39-40.2)	39.4 (38.5-40)
Duration of stay in malaria endemic area (yrs)	12 (6-21)	3.0 (0-20)
Duration of malaria symptoms before admission (days)	4 (3-28)	3.5 (1-10)
Antimalarial treatment before admission (n)	0	0
Laboratory data on admission		
Initial parasitemia (/μl)	23,460 (1,365-48,996)	34,124 (16,492-76,960)
Hematocrit (%)	36 (28.5-40.9)	41.2 (32-46.1)
Hemoglobin (g/dl)	11 (9.5-13.6)	14.0 (10.9-15.9)
Red blood cells (10^6/μl)	4.1 (3.2-5.29)	4.8 (4.2-5.3)
White blood cells (/μl)	5,600 (2,400-7,800)	5,600 (3,800-6,700)
Neutrophils (%)	62 (59-81)	77 (70-83)
Lymphocytes (%)	18 (17-30)	23 (19-41)
Platelets (10^3/μl)	59 (24-200)	69 (25-118)
Total protein (g/dl)	7.0 (6.8-7.5)	7.1 (5.9-7.8)
Albumin (g/dl)	3.9 (3.6-4.3)	4.1 (3.7-5.3)
SGOT (U/l)	30 (27-46)	39 (27-123)
SGPT (U/l)	28 (15-36)	39 (16-81)
Total bilirubin (mg/dl)	1.2 (1.0-2.2)	1.6 (1.2-2.7)
BUN (mg/dl)	33.0 (28.2-51.0)	45.2 (19.2-55.7)
Creatinine (mg/dl)	1.1 (0.9-1.5)	1.2 (1.1-1.4)
Glucose (mg/dl)	119 (92-133)	125 (92-170)
Response after treatment		
PCT (h)	36 (18-60)	48 (24-84)
FCT (h)	48 (42-72)	54 (42-72)
Recrudescence by day 42 (n)	0	0

*Hackett's method: grade 1: spleen was enlarged below the left costal margin about 2 cm.

DISCUSSION

In the present study, there were no differences in the pharmacokinetics of MQ when given at two different times, *ie,* 6 and 24 hours after the initial dose of DHA. Thus, the results from the study suggest that DHA had no influence on the kinetics of MQ when given concurrently. This finding is in agreement with that reported in a previous study in Vietnam where no pharmacokinetic interactions between artesunate and MQ were found (Hung *et al,* 2004*)*. No differences in pharmacokinetics for MQ were found when given as combination therapy with DHA either when DHA (300 mg) was given concurrently with MQ (750 mg), or

Table 2
Pharmacokinetic parameters of MQ when given as 750 mg at 0 (regimen-A) and 24 hours (regimen-B) after an oral dose of DHA in Vietnamese male patients with uncomplicated falciparum malaria. Data are presented as median (95%CI) values.

Pharmacokinetic parameters	Pharmacokinetics of mefloquine			
	Regimen-A		Regimen-B	
	n		n	
MQ dosage (mg/kg)		14.4 (13.9-16.7)	6	13.7 (12.7-14.2)
t_{lag} (h)	5	1.67 (0-2)	6	0.39 (0.1-1.9)
C_{max} (ng/ml)	5	1,969 (507-2,413)	6	1,907 (1,442-2,741)
t_{max} (h)	5	18 (4-48)	6	18 (4-24)
$t_{1/2\lambda}$ (h)	5	263 (236-414)	4	258 (210-327)
CL/F (l/h)	5	1.1 (1.0-3.5)	4	1.3 90.9-1.5)
CL/F (l/day/kg)	5	0.55 (0.5-1.5)	4	0.54 (0.4-0.7)
Vd/F (l/kg)	5	9.2 (7.8-38.2)	4	9.5 (5.4-12.0)
AUC_{0-96h} (ng.day/ml)	5	6,311 (1,595-8,177)	5	6,216 (4,455-8,812)
AUC_{0-168h} (ng.day/ml)	5	9,944 (2,493-12,524)	5	8,691 (97,080-12,927)
AUC_{0-336h} (ng.day/ml)	5	16,762 (4,861)	6	13,470 (9,361-19,360)
$AUC_{0-\infty}$ (ng.day/ml)	5	28,060 (9,037-30,446)	4	25,219 (21,506-33,182)
Duration of MQ levels above 500 ng/ml (days)	5	19.4 (0-22.1)	6	15.9 (10.9-23.8)

There are no differences between the pharmacokinetic parameters of MQ with the two regimens.

24 hours after DHA (300 mg) in malaria patients (Na-Bangchang *et al,* 2005). Furthermore, no interactions were seen between DHA and MQ in a crossover study in 10 healthy Thai males (Na-Bangchang *et al,* 1999). In contrast with these findings, DHA, artesunate and artemether were reported in some studies (Karbwang *et al*, 1994; Na-Bangchang *et al*, 1995; Hung *et al,* 1999) to alter the kinetics of MQ in combination regimens in malaria patients compared with that of the monotherapy regimen. The changes included a lower C_{max}, higher CL/F and higher Vd/F. However, the $t_{1/2z}$ of MQ in both combination and monotherapy was similar. The high inter-individual variability of MQ pharmacokinetics observed in this study are in accordance with several previous studies (Karbwang *et al* 1994; Na-Bangchang *et al*, 1995,1999; Hung *et al,* 1997,1999; Price *et al,* 1999). This variability together with a small sample size may also account for discrepancies observed in MQ pharmacokinetics among various studies. The $t_{1/2z}$ values for MQ in both monotherapy and combination therapy in malaria patients appears to be shorter than that in healthy subjects (Karbwang *et al,* 1994; Na-Bangchang *et al*, 1995,2005; Hung *et al*, 1999). For example, the median (95% CI) $t_{1/2z}$ observed in this study was 11 (10-17) days, which is significantly shorter than the $t_{1/2z}$ of 23 (22-39) days reported in Vietnamese healthy males (Hung *et al,* 1998). In addition, the C_{max} and the AUC_{0-168h} were significantly higher, while Vd/F was lower in malaria patients in this study compared to corresponding values in volunteers in a previous study (Hung *et al,* 1998). Similar results were reported in malaria patients following four DHA-MQ combination regimens (Na-Bangchang *et al,* 2005). Based on results observed in the present study along with that previously reported, it is concluded there are no significant differences in the pharmacokinetics of MQ when given at different

times in the combination regimens of malaria patients. The significant differences in the pharmacokinetics of MQ were often seen mainly between malaria patients and healthy subjects. The changes in C_{max}, CL/F and Vd/F of MQ in the combination regimens with artemisinin derivatives were associated with malaria severity rather than drug interactions. These changes may be due to distribution volume contraction and interruption of the enterohepatic cycle of MQ in malaria patients during the acute phase of malaria. In Vietnamese subjects, there were no differences in the t_{max} and the $AUC_{0-\infty}$ between malaria patients in our study and healthy volunteers. Our findings are in agreement with Na-Bangchang *et al* (2005) except for the t_{max} which was longer. Price *et al* (1999) found that MQ given in combination with artesunate at 72 hours (day 2) had a significantly higher $AUC_{0-\infty}$ compared to artesunate at 0 hour (day 0). The administration of MQ during the convalescent period (day 2) may improve the bioavailability of the drug. By that time, patients were often not febrile and the gut absorption was returning to normal.

Maintenance of whole blood MQ levels above 500 ng/ml ensures the therapeutic efficacy of MQ. A time period of 16.3 (0-23.8) days [median (95% CI)] was observed in this study, which is similar to a report in Thai patients following 25 mg/kg MQ (Price *et al,* 1999). One patient was noted to have a C_{max} of 504 ng/ml and a time period when MQ levels were maintained above 500 ng/ml of zero. This patient, nevertheless, responded well to treatment with no recrudescence during 42 days of follow-up. This may be explained by a high sensitivity of *P. falciparum* parasites in this particular case.

There was no recrudescence in any of the eleven patients in this study. Higher recrudescence rates (approximately 20%) was observed following 1-day combination regimens when artemisinin or artesunate were given with MQ in other studies (Hung *et al,* 1997,2004; Na-Bangchang *et al,* 2005). The dose of MQ given in the current study (15 mg/kg body weight) is similar to these studies but the duration artemisinin derivative (DHA) was given longer (2 days). This suggests that single day treatment with artemisinin derivatives may not be enough to clear parasites due to their short half-lives. Longer treatment courses for combination artesunate and MQ of 3 to 5 days are often used in Thailand (Price *et al,* 1999). Since the results of the current study show no interaction between MQ and DHA, it would be more practical to give MQ at least one day after the dose of artemisinin derivatives to improve patient compliance.

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