Pharmacokinetics of mefloquine in combination with sulfadoxine–pyrimethamine and primaquine in male Thai patients with falciparum malaria

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The pharmacokinetics of mefloquine (M) were studied in 59 male Thai patients with falciparum malaria. Mefloquine was administered alone (750 mg orally; group 1), or with primaquine (PQ, 45 mg; group 2), or in combination with sulfadoxine (1.5 g) + pyrimethamine (75 mg) (MSP; group 3), or as MSP + PQ (group 4). All patients in groups 1, 2 and 4 initially responded to treatment, but two patients from group 1 had RI recrudescent infections. One patient in group 3 failed to respond to treatment and was considered to have RII resistance, while a further patient from this group had RI recrudescence. The pharmacokinetic parameters for group 1 and group 3 were not significantly different. Co-administration of primaquine alone had no significant effect on the pharmacokinetics of mefloquine, but there was a statistically significant decrease in the terminal elimination half-life of mefloquine for group 4 relative to that for group 3.

Introduction

Mefloquine is an effective treatment for multidrug-resistant malaria (*1–5*); however, despite its widespread use in Thailand since 1984 there are a number of aspects of its pharmacokinetics that are poorly understood. Looareesuwan et al. have shown that the peak mefloquine concentrations in Thai patients with acute falciparum malaria who received a 250-mg dose were approximately three times higher than in healthy Caucasian volunteers; also, the apparent volume of distribution was smaller and the terminal half-life was significantly shorter in the Thai patients (*6*). However, it was not possible to determine whether ethnic or disease-related factors were responsible for these differences. Recently Karbwang et al. studied the kinetics of a single oral dose of mefloquine (750 mg) in Thai patients with falciparum malaria and compared the results with those of a previous study involving healthy Thai volunteers (*7, 8*). For patients and controls there were no significant differences in the peak plasma concentrations of mefloquine, time to peak concentration, area under the concentration–time curve, or apparent volume of distribution; however, the terminal half-life was significantly shorter in the patients. This study suggested therefore that malaria increased the rate of elimination of mefloquine, although the mechanism of the changes produced was not clear.

Mefloquine is currently marketed in combination with sulfadoxine–pyrimethamine, and Karbwang et al. have shown that in healthy Thai volunteers the combination mefloquine plus sulfadoxine–pyrimethamine has a slightly longer terminal half-life and mean residence time than mefloquine alone (*8*). It is important to ascertain whether this is also the case for patients with falciparum malaria.

Finally, in malaria clinics in Thailand mefloquine is used in conjunction with primaquine and there is therefore the potential for pharmacokinetic interaction between these two antimalarials. This is especially significant in the light of reports that primaquine inhibits hepatic microsomal enzymes both *in vitro* and *in vivo* in animals (*9–13*) and humans (*14–15*).

The present study reports on the pharmacokinetics of mefloquine when used in combination with sulfadoxine-pyrimethamine and/or primaquine.

Materials and methods

Patients

Adult (>15 years of age) male patients with acute falciparum malaria (asexual forms of *Plasmodium falciparum* evident in blood smears) were included in the study. The patients were admitted to the Hospital for Tropical Diseases, Bangkok, Thailand, and their written informed consent was obtained. The study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University.

Patients were excluded if they had a history of recent antimalarial treatment; a history of gastrointestinal disease with malabsorption or previous

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surgery to the upper gastrointestinal tract; asexual parasitaemia of >50%; or impaired consciousness, jaundice, oliguria, or vomiting that required parenteral treatment before starting antimalarial therapy. Patients were also excluded if chloroquine (Wilson and Dill–Glazko tests) or sulfadoxine (lignin test) was detected in their urine. Pretreatment blood samples that contained either mefloquine or quinine (as estimated by high-performance liquid chromatography (HPLC)) were excluded from the data analysis.

The patients were examined clinically in the hospital prior to commencing therapy and the data obtained were recorded on standard forms; the examination included body weight, height, and temperature. Baseline laboratory investigations included parasite counts, complete blood examination, determination of serum chemistry, as well as screening tests for plasma quinine and mefloquine.

Treatment groups

The study was an open, randomized trial involving recruitment into the groups outlined below.

- Group 1: 750 mg mefloquine (M) (base tablets each containing 250 mg mefloquine).
- Group 2: 750 mg mefloquine + 45 mg primaquine (PQ).
- Group 3: MSP (750 mg mefloquine, 1500 mg sulfadoxine (S), 75 mg pyrimethamine (P)).
- Group 4: MSP (as above) + 45 mg PQ.

The drugs were administered as single doses.

Study design

Blood samples were collected using an indwelling intravenous Teflon catheter kept patent with heparinized saline. The samples were taken pre-dose, and at 1, 2, 4, 8, 12, 24, 48, 72, and 96 hours, as well as at 7, 14, 21, 28, and 42 days after the dose. Samples were collected into heparinized tubes and the plasma separated within 30 minutes; this was stored in plastic tubes at −20 °C until analysed.

Parasite counts were made twice daily until parasitaemia had cleared, then daily until 28 days, and again on day 42. Patients' temperatures were measured every 4 hours.

A full blood examination and determination of serum chemistry were carried out on days 1, 4, 7, 14, 28, and 42. The clinical examinations were performed daily for 7 days, then on days 14, 21, 28, and 42.

Determination of mefloquine concentration

Mefloquine was determined by HPLC using the method described by Riviere et al. (*16*). The lower limit of detection of the assay, which was defined as the minimum concentration that could be determined with a precision of better than 10%, was 20 ng/ml. The inter-assay coefficient of variation was 4.1% at a concentration of 100 ng/ml and 5.7% at 600 ng/ml.

Mefloquine pharmacokinetic analysis

The peak concentration of mefloquine (C_{max}) and the time to peak concentration (t_{max}) were obtained. The area under the plasma concentration–time curve (AUC) was calculated using the linear trapezoidal rule. The estimated area for the last sampling time to t_∞, the first-order elimination rate constant λ_k and the half-life ($t_{1/2}$) were calculated using conventional methods (*17*). The mean residence time of mefloquine in the body (MRT) was calculated using the expression:

$$MRT = \int_0^\infty tC\,dt \Big/ \int_0^\infty C\,dt$$

where t is time (in days) and C is the plasma concentration of mefloquine.

The apparent volume of distribution (V_z) was calculated using the expression:

$$V_z = f \times \text{Dose} \times t_{1/2}/(AUC \times 0.693)$$

The clearance (Cl) was calculated by dividing the dose by the AUC.

Since the bioavailability (f) of mefloquine was not known, values for V_z/f and Cl/f were obtained.

Statistical analysis

All the pharmacokinetic parameters were analysed using a two-factor analysis of variance. Since all patients received mefloquine, the factors were the two (additional) drug combinations (MSP and MSP + PQ) and their interaction. Most of the variables measured had skewed distributions and for these, log-transformed data were used. Significance levels were obtained using Student's t-tests and confirmed using an unpaired Wilcoxon's rank sum test. The results are presented as means ± standard deviations.

Results

Clinical and parasitological responses

A total of 59 male patients were studied. All reported a history of fever lasting 1–3 days and all but one patient was febrile (Table 1). Altogether, 57 patients were followed up for 42 days; one patient (from group 2) was followed up for 21 days; and one (from group 3) for 29 days.

In group 1 (mefloquine alone) all patients responded to treatment, with mean fever and parasite clearance times of 38.0 ± 20.2 hours and 66.0 ± 14.1

Table 1: **Results of the baseline laboratory investigation of patients in the various treatment groups on admission to the study**

	Mean ± S.D.[a]			
	Mefloquine (group 1)	Mefloquine + PQ (group 2)	MSP (group 3)	MSP + PQ (group 4)
Weight (kg)	52.0 ± 4.6	54.8 ± 3.3	56.7 ± 2.9	53.9 ± 4.3
Temperature (°C)	38.3 ± 0.9	38.8 ± 0.9	38.4 ± 0.8	37.8 ± 0.7
Haematocrit (%)	35.6 ± 7.3	36.2 ± 5.4	37.6 ± 6.7	33.5 ± 6.0
White blood cell count (× 10^9/l)	5496 ± 2038	6171 ± 1805	5649 ± 1186	5476 ± 2261
Parasitaemia (× 10^9/l)	19 076 (3850–185 850)[b]	24 223 (4900–188 160)	17 745 (3380–193 900)	15 330 (4470–36 680)
Serum bilirubin (mg/dl)	1.1 ± 0.4	1.1 ± 0.6	0.9 ± 0.2	1.0 ± 0.6
Serum creatinine (mg/dl)	1.2 ± 0.7	1.0 ± 0.2	1.1 ± 0.2	1.0 ± 0.1

[a] M = mefloquine; MSP = mefloquine + sulfadoxine–pyrimethamine; M + PQ = mefloquine + primaquine; MSP + PQ = mefloquine + sulfadoxine–pyrimethamine + primaquine.

[b] Figures in parentheses are the range.

hours, respectively. Two patients who had no history of vomiting after taking mefloquine, underwent recrudescence on day 21 and day 32 (symptomatic cases); their plasma concentrations of mefloquine are shown in Table 2.

All patients in group 2 (M + PQ) responded to treatment, with mean fever and parasite clearance times of 47.3 ± 17.9 hours and 65.5 ± 16.2 hours, respectively.

In group 3 (MSP), all but one patient responded to treatment, with mean fever and parasite clearance times of 55.7 ± 28.4 hours and 73.6 ± 36.9 hours, respectively. The patient who failed to respond to treatment was considered to have type II resistance and data for this patient were excluded from the analysis of fever and parasite clearance times. This patient had asymptomatic parasitaemia until day 17, when a second dose of MSP was administered. Among patients who responded initially to treatment, one also had recrudescence on day 21. The plasma concentrations of mefloquine for these two patients are shown in Table 2.

All patients in group 4 (MSP + PQ) responded to treatment, with mean fever and parasite clearance times of 54.4 ± 34.6 hours and 60.1 ± 7.0 hours, respectively.

Adverse effects

Adverse effects were monitored daily by administering a questionnaire for 1 week, and then weekly until day 42 (6 weeks). The clinical examinations, serum chemistry profiles, and blood counts were normal from day 7 onwards.

Three patients from group 1, two from group 2, and four from group 3 vomited after taking the medication. The peak plasma concentrations of mefloquine and time of vomiting are shown in Table 3. One patient from group 4 had diarrhoea. No other adverse effects were observed. All episodes of vomiting occurred 1 hour or later after taking the drugs, with the exception of one patient who vomited after 30 minutes. The latter patient had the lowest peak plasma concentration in the study.

Pharmacokinetics of mefloquine

Selected pharmacokinetic parameters for mefloquine are shown in Table 4. There was a considerable variation in the peak plasma concentrations within each group (group 1, 1591–3904 ng/ml; group 2, 1095–3754 ng/ml; group 3, 766–4513 ng/ml; group 4,

Table 2: **Plasma concentrations of mefloquine in the four patients with recrudescent infections**

Treatment group[a]	Peak mefloquine concentration (ng/ml)	Day of recrudescence (days after treatment)	Mefloquine concentration at the time of recrudescence (ng/ml)
Mefloquine (RI)	2437	D21	361
Mefloquine (RI)	2663	D32	270
MSP (RII)[b]	1663	—	401
MSP (RI)[c]	2369	D21	301

[a] The type of recrudescence is shown in parentheses; MSP = mefloquine + sulfadoxine–pyrimethamine.

[b] Patient vomited 2.5 hours after receiving the therapy.

[c] Patient vomited 6 hours after receiving the therapy.

Table 3: **Peak plasma concentrations of mefloquine in patients who vomited after receiving the treatment**

Treatment group[a]	Peak plasma concentration (ng/ml)	Time of vomiting (hours' post-dosing)
Mefloquine	1592	1
Mefloquine	1856	1
Mefloquine	3084	3
Mefloquine + PQ	1095	7
Mefloquine + PQ	1534	30
MSP	1663[b]	2.5
MSP	1483	1.5
MSP	766	0.5
MSP	2369[c]	6

[a] PQ = primaquine; MSP = mefloquine + sulfadoxine–pyrimethamine.
[b] Treatment failure (RII). [c] Treatment failure (RI).

1213–4282 ng/ml). All groups exhibited inter-individual variation in the time to peak concentration (4–48 hours). The differences between the peak plasma concentrations and times to peak concentration were not significantly different for the various groups.

There were no significant differences in the elimination half-life ($t_{1/2}$), elimination rate constant (λ_k), area under the curve (AUC), mean residence time (MRT), apparent oral clearance (Cl/f), and apparent volume of distribution (V_z/f) for patients who received mefloquine alone versus those who received MSP alone. Co-administration of primaquine alone had no significant effect on the pharmacokinetics of mefloquine but there was a statistically significant decrease in the elimination half-life ($t_{1/2} = 10.4 \pm 1.9$ days) for group 4 (MSP + PQ) compared with that for group 3, who received MSP alone (12.7 ± 2.1 days; $P < 0.005$). However, the other pharmacokinetic parameters were not significantly different.

Discussion

Four patients showed resistance to mefloquine — two in group 1 (mefloquine alone) and two in group 4 (MSP). The peak concentrations of mefloquine in these patients lay within the range exhibited by those who responded to the drug. It can therefore reasonably be claimed that these four patients had mefloquine-resistant falciparum malaria. The cure rate found in the study was 93.2%, a good response to mefloquine.

The patient who gave an RII response to treatment had a mefloquine plasma level of 401 ng/ml prior to receiving a second dose, but the results from the *in vitro* sensitivity test for mefloquine estimated the minimum therapeutic concentration to be 0.1 pmole/μl (40 ng/ml). The minimum concentration of mefloquine required to cure chloroquine-resistant falciparum malaria in Thailand remains uncertain. Indeed, it is difficult to define such a level in view of confounding factors, such as immunity; further studies, particularly

Table 4: **Selected pharmacokinetic parameters for mefloquine for the study subjects in the various treatment groups**

	Mean ± S.D.[a]			
	Mefloquine (group 1) ($n = 15$)	Mefloquine + PQ (group 2) ($n = 14$)	MSP (group 3) ($n = 16$)	MSP + PQ (group 4) ($n = 14$)
Time to peak concentration (hours)	16.9 ± 13.2 (6–48)[b]	14.1 ± 8.1 (4–24)	19.0 ± 13.3 (6–48)	23.4 ± 14.7 (8–48)
Peak concentration (ng/ml)	2690 ± 672 (1591–3904)	2303 ± 854 (1095–3754)	2559 ± 1107 (766–4513)	2756 ± 1047 (1213–4282)
Half-life (days)	11.7 ± 2.0 (8.1–15.8)	11.4 ± 1.3 (8.9–13.9)	12.7 ± 2.1 (9.5–16.9)	10.4 ± 1.9[c] (7.0–12.9)
Elimination rate constant (day^{-1})	0.061 ± 0.010 (0.044–0.085)	0.061 ± 0.007 (0.050–0.078)	0.056 ± 0.010 (0.041–0.073)	0.069 ± 0.015 (0.054–0.099)
Area under the curve (μg/ml × days)	27.0 ± 8.2 (14.3–43.7)	24.9 ± 9.9 (13.4–44.8)	24.3 ± 8.7 (12.9–38.1)	25.6 ± 8.7 (12.7–46.4)
Mean residence time (days)	16.3 ± 3.7 (11.6–23.3)	15.5 ± 1.8 (11.8–18.2)	16.4 ± 3.2 (12.3–22.6)	14.1 ± 3.3 (9.2–21.4)
V_z/f (litres)	500 ± 135 (322–791)	587 ± 265 (285–973)	667 ± 322 (288–1348)	511 ± 246 (238–1089)
Cl/f ($l.day^{-1}$)	30.6 ± 10.0 (17.1–52.4)	34.9 ± 13.7 (16.8–56.0)	35.7 ± 14.1 (19.7–58.1)	33.9 ± 13.3 (16.2–60.9)

[a] MSP = mefloquine + sulfadoxine–pyrimethamine; PQ = primaquine.
[b] Figures in parentheses are the range.
[c] Significantly different from MSP alone; $P < 0.005$.

of all cases of therapeutic failure are required to elucidate this.

Of the patients who vomited after taking the medication, all except two responded to treatment. It is interesting that only one patient had an atypically low peak plasma concentration of mefloquine after vomiting, which suggests that a second dose of the drug under such circumstances may not always be necessary. Since in most cases vomiting occurred within a few hours of taking the drugs, the most likely explanation is local gastric irritation. Further studies, specifically designed to study the relationship of vomiting to the absorption of mefloquine, are, however, needed to provide guidelines for deciding when repeat dosing is necessary.

The finding that there were no significant differences in the pharmacokinetic parameters for male patients who received mefloquine alone and MSP alone indicates that the presence of sulfadoxine and pyrimethamine do not significantly influence the pharmacokinetics of mefloquine. This contrasts with the results of a study of Thai male volunteers, for whom the group that received MSP exhibited a 24% increase in the half-life of mefloquine and a 27% increase in the *MRT* compared with the group given mefloquine alone; there is no clear explanation for this difference between the patient and volunteer studies. It is probably more important to establish first the basis of the clear difference in the elimination kinetics of mefloquine between patients and volunteers. The half-life of mefloquine for the male volunteers was 15.4 ± 0.9 days (*7*), whereas for the patients in the present study it was 11.7 ± 1.9 days — a 25% decrease for the patients. If MSP was used instead of mefloquine alone, the respective half-lives were 19.1 ± 4.4 days and 12.7 ± 2.1 days for volunteers and patients, respectively. An examination of the possible role of enterohepatic recycling in the elimination of mefloquine should be carried out, since this mechanism may be altered in malaria patients. It is very interesting to note that in dogs mefloquine does not undergo enterohepatic recycling and that in dogs the half-life is shorter than in other animals or humans (G. Friedrich, personal communication, 1988).

Co-administration of primaquine caused a statistically significant decrease ($P < 0.05$) in the elimination half-life of mefloquine in group 4 (MSP + PQ; $t_{1/2} = 10.4 \pm 1.9$ days) compared with that for group 3 (MSP alone; 12.7 ± 2.1 days). This may have arisen because of the ability of primaquine to inhibit the metabolism of sulfadoxine, thus maintaining its concentration for longer in the body. Sulfadoxine could then interfere with the normal composition of bacterial flora, thus interrupting the enterohepatic recycling of mefloquine.

The concentrations of mefloquine metabolites in the different groups were not investigated. Recently Franssen et al. showed that the plasma concentrations of the carboxylic acid metabolite of mefloquine were 2–3 times greater than those of mefloquine itself within 2 days in healthy Caucasian volunteers. However, it is unlikely that the metabolite contributes to therapeutic response (based on *in vitro* IC_{50} determinations with three strains of *P. falciparum* (*18*)); it is therefore of considerable importance to determine whether the metabolite contributes to the side-effects (*19*).

A further consideration is whether the sulfadoxine–pyrimethamine component confers any advantage over mefloquine alone, in view of the potential for serious sulfonamide toxicity (*20*). If co-administration of sulfadoxine–pyrimethamine delays the development of resistance, as has been shown in rodent malaria (*21*), its benefits may override its potential toxicity. Recently, however, White has argued that the prevention of mefloquine resistance in falciparum malaria by sulfadoxine–pyrimethamine is unlikely, since mefloquine needs to be protected when malaria parasites encounter sub-inhibitory blood concentrations, i.e., many weeks after single-dose treatment (*22*). This does not happen because in humans sulfadoxine and pyrimethamine have much shorter half-lives than in rodents. Thus, a low concentration of mefloquine persists in the blood for long periods, unprotected by the other drugs. Serious consideration therefore has to be given to the benefit:risk ratio for patients who receive MSP rather than mefloquine alone.

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Résumé

Pharmacocinétique de la méfloquine en association avec la sulfadoxine–pyriméthamine et la primaquine chez des Thaïlandais atteints de paludisme à falciparum

La pharmacocinétique de la méfloquine (M) a été étudiée chez 59 Thaïlandais de sexe masculin atteints de paludisme à falciparum. Elle était administrée soit seule (750 mg par voie orale, groupe 1), soit avec de la primaquine (PQ, 45 mg, groupe 2), soit en association avec de la sulfadoxine (1,5 g) et de la pyriméthamine (75 mg) (MSP, groupe 3), soit encore en association multiple

MSP + PQ (groupe 4). Tous les sujets des groupes 1, 2 et 4 répondaient au traitement, bien qu'on ait observé chez deux malades du groupe 1 une recrudescence, le 21e jour chez l'un et le 32e jour chez l'autre. L'absence de réponse au traitement chez un sujet du groupe 3 a été attribuée à une résistance de type II; un autre malade de ce groupe a présenté une recrudescence au 21e jour. Bien que neuf malades aient vomi après avoir pris l'antipaludique, leur pic plasmatique de méfloquine ne différait pas sensiblement de celui des autres malades. On n'a observé aucune différence significative de la demi-vie d'élimination, de la constante d'élimination (λ_z), de l'aire sous la courbe, du temps de résidence moyen, de la clairance orale apparente, du volume apparent de distribution, du pic de concentration, ni du délai d'apparition du pic de concentration chez les sujets ayant reçu la méfloquine + PQ ou l'association MSP. L'administration simultanée de primaquine était sans effet significatif sur la pharmacocinétique de la méfloquine; en revanche, on observait une baisse statistiquement significative de la demi-vie d'élimination chez les sujets du groupe MSP + PQ ($t_{1/2} = 10{,}4 \pm 1{,}9$ jours) par rapport au groupe MSP sans PQ ($t_{1/2} = 12{,}7 \pm 2{,}1$ jours; $P \leqslant 0{,}005$); les autres paramètres cinétiques ne différaient pas notablement entre ces deux groupes. Cette différence pourrait s'expliquer par l'aptitude de la primaquine à inhiber le métabolisme de la sulfadoxine, ce qui permettrait le maintien de concentrations élevées de cette dernière, et par suite freinerait le recyclage entérohépatique de la méfloquine.

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