Pharmacokinetics of mefloquine alone or in combination with artesunate

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A randomized comparative trial of the pharmacokinetics and pharmacodynamics of oral doses of mefloquine and of mefloquine in combination with artesunate was carried out on 20 Thai male patients with acute, uncomplicated falciparum malaria. The patients were randomized to receive either mefloquine alone (8 patients; 1250 mg of mefloquine—initial dose, 750 mg; followed 6 hours later by 500 mg), or in combination with oral artesunate (12 patients—initial dose, 200 mg of artesunate; followed by 750 mg and 500 mg of mefloquine 6 hours and 12 hours later, respectively).

The patients who received mefloquine alone all showed initially good responses to the treatment, with mean ± SD values for the fever clearance time (FCT) and parasite clearance time (PCT) of 44.7 ± 43.1 hours and 82.3 ± 52.3 hours, respectively. Two patients had recrudescences on day 20 and day 31 (RI response). The cure rate was 75%, and one patient had Plasmodium vivax *in his peripheral blood on day 52.*

The patients who received the combination treatment were clinically markedly improved, with a relatively shorter FCT (31.2 ± 12.4 hours) and significantly shorter PCT (47.5 ± 19.6 hours). Four had recrudescences on days 12, 18, 26 and 33; the cure rate was 66%.

Artesunate caused three significant changes in mefloquine pharmacokinetics: a decrease in the maximum concentration (C_{max}: 1623 ng.ml^{-1} versus 2212 ng.ml^{-1}); an increase in the clearance rate (Cl/f:2.9 ml.min^{-1}.kg^{-1} versus 1.1 ml.min^{-1}.kg^{-1}); and an expansion of the volume of distribution (Vd_z/f: 31.8 l.kg^{-1} versus 25.0 l.kg^{-1}).

Multiple drug-resistant strains of *Plasmodium falciparum* are now increasing and spreading in Thailand (*1*). Artesunate is very effective against multiple drug-resistant falciparum malaria (*2, 3*); however, the duration of treatment needs to be at least 5 days to achieve a cure rate >90% and this is a limiting factor for its use because of poor patient compliance. The combination of this potent antimalarial with drugs with a longer half-life, such as mefloquine, may improve the compliance and the cure rate. It has been demonstrated *in vitro* that the combination of artesunate with mefloquine produces a synergistic effect (*4*). We report in this article the efficacy and pharmacokinetics of mefloquine in combination with artesunate compared with those of mefloquine alone in patients who have chloroquine-resistant falciparum malaria.

Materials and methods

Patients. A total of 22 adult Thai male patients with acute, uncomplicated falciparum malaria (asexual form parasitaemia <5%), aged 17–48 years and weight range 45–70 kg, with no history of liver or kidney diseases, were recruited into the study. No other drugs were taken by the patients during the study. The written informed consent to participate in the study was obtained from all the patients. The study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

Each patient underwent a physical examination, routine blood tests and blood biochemistry investigations, plain chest X-ray, urine analysis and an electrocardiogram. All patients were admitted to the Bangkok Hospital for Tropical Diseases for 42 days.

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Treatment. The patients were randomized into two groups (A and B) to receive two drug regimens as follows:

— Group A (8 patients): an initial oral dose of 750 mg of mefloquine (Lariam®, Hoffmann-La Roche; 250 mg per tablet) followed 6 hours later by 500 mg.

— Group B: an initial oral dose of 200 mg of artesunate followed by mefloquine (750 mg and 500 mg, 6 hours and 12 hours after the artesunate, respectively).

The drugs were administered with a glass of water under supervision.

Patients who exhibited treatment failure received the standard regimen of quinine (600 mg three times per day) plus tetracycline (250 mg four times per day) for 7 days.

Parasite counts. Parasite counts were performed twice daily until negative, then once daily until day 42 of the study.

Haematological and biochemical investigations. Blood tests and blood biochemistry investigations were performed on days 0, 2, 4, 7, then weekly until day 42. These included complete blood count, liver function tests (serum aspartate aminotransferase (SGOT), serum alanine aminotransferase (SGPT), alkaline phosphatase, serum protein), kidney function tests (blood urea nitrogen, creatinine, electrolytes), blood glucose, and urine analysis.

Blood for mefloquine concentrations. Blood samples were collected for determination of mefloquine concentrations at 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, and 42 hours after the initial dose of mefloquine was administered, and then on days 2, 3, 4, 5, 7, 14, 21, 28, 35, and 42.

Adverse effects. All adverse reactions during the study were recorded with the date and time when they occurred and disappeared. These included changes to the gastrointestinal, central nervous, cardiovascular, dermatological, and haematological systems as well as other changes possibly attributable to mefloquine or artesunate.

Blood pressure measurements were performed at 4-hour intervals during the first week, then daily until day 42 of the study.

Pharmacokinetic analysis. The whole blood mefloquine concentrations were determined using high-performance liquid chromatography (HPLC) (*6*) and the concentration–time profiles were analysed using an iterative, nonlinear curve-fitting program (PCNONLIN, Metzler & Weiner, 1984). A multiple-dosing approach was used to fit a two-compartment model to the unweighted data.

The clearance (Cl/f) was calculated by dividing the dose by the total area under the concentration–time curve (AUC) (calculated using the trapezoidal rule). The apparent volume of the distribution (Vd_z/f) was derived using the expression:

$$Vd_z/f = (\text{dose} \times T_{1/2})/(AUC \times 0.693)$$

where $T_{1/2}$ is the biological half-life of mefloquine.

Data analysis. Patients were included for efficacy assessment when they had completed the 42-day study period. The efficacy (parasite clearance time (PCT), fever clearance time (FCT) (cure rate) and adverse effects for the two therapeutic regimens were compared using the χ^2 test.

The Mann–Whitney U test was used to compare the mefloquine concentrations and pharmacokinetic parameters obtained for the two treatment groups.

Results

A total of 20 patients with acute uncomplicated falciparum malaria were recruited into the study. The clinical data and baseline laboratory investigations on admission (Table 1) were comparable for the mefloquine alone and mefloquine plus artesunate groups.

Clinical response

Group A (mefloquine alone). All patients (n = 8) showed good initial response to the treatment (mean ± SD values: FCT = 44.7 ± 43.1 hours; PCT = 82.3 ± 52.3 hours). Two patients had recrudescences on day 20 and day 31 (RI response); the former vomited and had diarrhoea on day 1. The cure rate was 75%. The peripheral blood of one patient exhibited *P. vivax* on day 52.

Table 1: **Admission clinical data, parasite clearance time (PCT), and fever clearance time (FCT) in patients receiving mefloquine alone and in combination with artesunate**

	Mefloquine alone (n = 8)	Mefloquine + artesunate (n = 12)
Age range (years)	17–48	19–40
Weight range (kg)	47–61	49–69
Mean haematocrit ± SD (mg %)	38.1 ± 4.3	33.1 ± 5.2
Mean WBC ± SD (per µl)[a]	5149 ± 2332	5850 ± 1697
Geometric mean admission parasitaemia (per µl)	20 893	31 091
Mean PCT ± SD (hours)[b]	82.3 ± 52.3	47.5 ± 19.6
Mean FCT ± SD (hours)	44.7 ± 43.1	31.2 ± 12.4

[a] WBC = white blood cell count.
[b] Significantly different at P <0.01 (Mann–Whitney U test).

Group B (artesunate + mefloquine). All patients (n = 12) responded rapidly to the treatment (mean ± SD values: FCT = 31.2 ± 12.4 hours; PCT = 47.5 ± 19.6 hours). Four patients had recrudescences on days 12, 18, 26, and 33; the patients exhibiting early recrudescence (on days 12 and 18) vomited excessively immediately after taking the three mefloquine tablets. One patient had diarrhoea four times on day 1. The cure rate was 66%. *P. vivax* infection was not found in any of the patients during follow-up.

The patients on the combination treatment were clinically markedly improved on the following days with relatively shorter FCTs and significantly shorter PCTs (P = 0.01).

Adverse effects

The adverse effects were similar in both groups and consisted of nausea, vomiting, diarrhoea, dizziness, and bradycardia. Bradycardia occurred from day 3 onwards, and the lowest heart rate was found on day 6. None of the subjects showed any sign of neuropsychiatric reactions, and no significant changes in complete haematological or blood biochemistry investigations were observed throughout the study period.

Whole blood mefloquine concentrations

The mean whole blood mefloquine concentrations in both groups (excluding two patients who vomited excessively within an hour of taking mefloquine) are shown in Fig. 1. The mefloquine concentrations were higher in the patients who received this drug alone.

The mefloquine concentrations in patients with early recrudescence (on day 12 and day 18) who vomited excessively immediately after receiving the drugs (mefloquine + artesunate group) were lower than the concentrations in those with sensitive responses in either regimen (Fig. 2).

Fig. 1. **Mean whole blood mefloquine concentration–time profiles in the mefloquine alone and mefloquine + artesunate groups** (excluding 2 patients who vomited within 1 hour of receiving mefloquine).

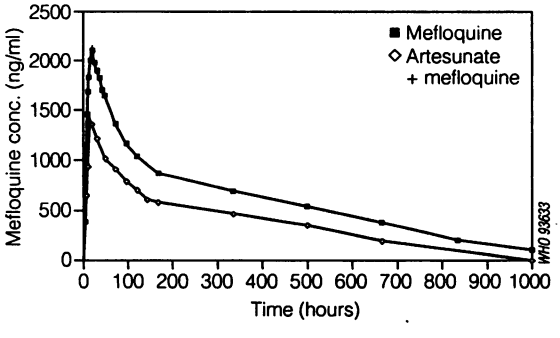
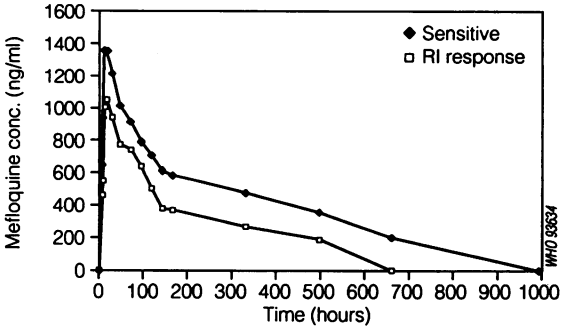


Fig. 2. **Mean whole blood mefloquine concentration–time profiles for patients with early recrudescence and sensitive responses in the combined therapy group.**



The pharmacokinetic parameters for mefloquine from both groups are shown in Table 2. The maximum concentration (C_{max}) was higher for the mefloquine alone group (P <0.05), whereas the clearance was faster (P <0.05) and the volume of distribution was greater (P <0.05) for the combination therapy group.

Discussion

The rapid action of artesunate against chloroquine-resistant falciparum malaria has been reported in studies carried out in China (*7*) and Thailand (*2, 3*), clearing 95% of parasitaemia within 24 hours, even with a single dose (*2, 3*). The only problem associated with the use of artesunate is the high recrudescent rate (RI response). There is an association between the duration of treatment and the curative outcome. With a one-day treatment course, the recrudescent rate was 100%, whereas with a longer treatment course the cure rate improved regardless of the total dose (*2, 3*). The duration of treatment needs

Table 2: **Pharmacokinetic parameters for mefloquine in volunteers receiving mefloquine alone or mefloquine + artesunate**

Pharmacokinetic parameter	Mean ± SD for: Mefloquine alone	Mefloquine + artesunate
C_{max} (ng.ml^{-1})	2212 ± 513	1623 ± 388
T_{max} (hours)	20.3 ± 5.2	15.0 ± 3.0
$T_{1/2ab}$ (hours)[a]	5.1 ± 0.9	3.7 ± 1.8
AUC (μg.ml^{-1}.day)	17.2 ± 6.4	12.8
$T_{1/2}$ (days)	11.9 ± 2.7	11.0 ± 7.0
Cl/f (ml.min^{-1}.kg^{-1})[b]	1.1 ± 0.50	2.9 ± 2.6
Vd_z/f (l.kg^{-1})[b]	25.0 ± 6.0	31.8 ± 5.1

[a] $T_{1/2ab}$ = absorption half-life.

[b] Significantly different at P <0.05 (Mann-Whitney U test).

to be at least 5 days to achieve a cure rate of over 90%. However, in practice, a course of treatment lasting more than 3 days is unlikely to be successful because of compliance difficulties, since patients feel better the first day following treatment. The combination artesunate plus mefloquine thus exploits artesunate's ability to clear parasitaemia quickly and hence rapidly improve the clinical symptoms, while retaining the full schizontocidal effect resulting from the slower action of mefloquine (pharmacodynamic synergism). This effect should prevent recrudescence and thus improve the cure rate. The duration of treatment from the combined regimen is therefore shorter than that with artesunate alone.

In our study, an initial dose of 200 mg of artesunate followed by 750 mg and 500 mg of mefloquine, respectively, 6 hours and 12 hours later shortened the FCT and PCT and rapidly improved the clinical symptoms. However, contrary to expectation, there appeared to be a pharmacokinetic interaction which lowered the mefloquine concentrations. The action of mefloquine is concentration-dependent. The concentrations of mefloquine on the first two days of treatment in patients with sensitive responses were significantly higher than those for patients with treatment failure (*8*). With the increasing occurrence of mefloquine-resistant strains of *P. falciparum*, higher blood mefloquine concentrations are required to achieve cure. In our study the mefloquine concentrations among patients in the mefloquine-alone group were higher than among those in the combination group; this seems to have clinical significance, and may explain the relatively better cure rate obtained with the single therapy regimen (75% versus 66%). In this case, the pharmacokinetic interaction (antagonistic effect) therefore overrides the pharmacodynamic interaction (synergistic effect) of the combination.

Since mefloquine is highly protein-bound (*9*), the lower concentrations that resulted when it was taken 6 hours after artesunate could arise because of competition for protein binding sites between mefloquine and artesunate or its metabolite(s), resulting in higher free mefloquine concentrations and as a consequence, a wider mefloquine concentration distribution. Free mefloquine can be cleared faster. This explanation is supported by the larger volume of distribution and faster clearance in the patients who received the combined regimen relative to those patients who received mefloquine alone. Alternatively, the decrease in mefloquine concentration could have resulted from the reduction in its oral bioavailability, induced by artesunate. Although, the available pharmacokinetic data for intravenous artesunate indicate that it has a short biological half-life (a few minutes), it is not clear whether this results from the parent compound itself or from its metabolite(s), since the effect on mefloquine was still observed 6 hours after artesunate has been administered.

When used in combination with artesunate, mefloquine should therefore be given when artesunate or its metabolite(s) are virtually cleared from the circulation. With the limited available information on the pharmacokinetics of oral artesunate, it may, however, be difficult to determine when mefloquine should be administered. Administration of mefloquine 24 hours after artesunate may be the most optimal timing; nevertheless, a drug interaction study should also be carried out in this connection.

The principal adverse effects found in the study were mainly gastrointestinal, and were comparable in both groups. Most of the patients in the mefloquine-alone group vomited a few hours after receiving the drug. In contrast, in the combined regimen group, two patients vomited within an hour of receiving the first dose of mefloquine, thus affecting its concentration and this could have been responsible for the treatment failure. These findings are in agreement with those we have reported previously, where early vomiting (within the first hour) but not late vomiting influenced the bioavailability of mefloquine (*10*).

Use of the combination artesunate + mefloquine therefore improves the clinical symptoms and may even prevent complications or the development of severe malaria, since its use can clear more than 95% of the existing parasitaemia within 24 hours, a capability not exhibited by other antimalarials. After artesunate's rapid action, mefloquine circulates in the blood long enough to act on the remaining parasites. However, the pharmacokinetic interaction which lowers the concentration of mefloquine reduces its efficacy. It is therefore essential to determine the optimum time to administer mefloquine if the combination is to be used, for which further studies are needed.

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Résumé

Pharmacocinétique de la méfloquine administrée seule ou en association avec l'artésunate

Un essai comparatif randomisé de la pharmacocinétique et de la pharmacodynamique de doses

orales de méfloquine seule et de méfloquine associée avec l'artésunate a été réalisé sur 20 Thaïlandais de sexe masculin atteints de paludisme à falciparum aigu non compliqué. Les sujets ont été répartis par tirage au sort dans un groupe recevant la méfloquine seule (8 sujets; 1250 mg de méfloquine: une dose initiale de 750 mg, puis 500 mg 6 heures plus tard) ou dans un groupe recevant la méfloquine associée à l'artésunate par voie orale (12 sujets; une dose initiale de 200 mg d'artésunate, puis une dose de 750 mg de méfloquine au bout de 6 heures et une dose de 500 mg de méfloquine au bout de 12 heures).

Les sujets ayant reçu la méfloquine seule ont tous présenté une bonne réponse initiale au traitement, avec des valeurs moyennes ± ET du temps de disparition de la fièvre de 44,7 ± 43,1 heures et du temps de disparition de la parasitémie de 82,3 ± 52,3 heures. Deux sujets ont présenté une recrudescence les jours 20 et 31 (réponse de type RI). Le taux de guérison était de 75%; chez un sujet, on a trouvé des *Plasmodium vivax* dans le sang périphérique le jour 52.

Les sujets ayant reçu l'association étaient plus rapidement améliorés: disparition plus rapide de la fièvre (31,2 ± 12,4 heures) et disparition sensiblement plus rapide de la parasitémie (47,5 ± 19,6 heures). Quatre sujets ont eu une recrudescence les jours 12, 18, 26 et 33; le taux de guérison était de 66%.

L'artésunate provoquait trois modifications significatives de la pharmacocinétique de la méfloquine: une diminution de la concentration maximale (C_{max}: 1623 ng/ml contre 2212 ng/ml); une augmentation de la clairance (Cl/f: 2,9 ml/min par kg contre 1,1 ml/min par kg), et enfin une augmentation du volume de distribution (Vd_z/f: 31,8 l/kg contre 25,0 l/kg).

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