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Single dose artemisinin–mefloquine versus mefloquine alone for uncomplicated falciparum malaria

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Abstract

The efficacy of the combination of a single oral dose of 500 mg artemisinin with a single 500 mg oral dose of mefloquine (AM) in the treatment of uncomplicated falciparum malaria was compared to mefloquine therapy alone (M) in a double-‘blind’ randomized study in an endemic area in the south of Viet Nam where single low dose treatment was employed and where mefloquine had been recently introduced. 231 patients, 117 AM and 114 M, were studied. Failure of therapy occurred in 1 AM patient and in 3 M patients. The radical cure rate was 84% for the AM regimen and 65% for the M regimen ($P=0.002$). Recrudescence (including an unknown percentage of reinfections) occurred in 15% of AM patients and in 30% of M patients ($P=0.01$). The mean parasite clearance time was 40 h (SD=16) for AM and 60 h (SD=27) for the M regimen ($P=0.0001$). No effect of artemisinin was noted on gametocytes present on admission, but new gametocytes developed less frequently in the AM group. The addition of a single dose of 500 mg artemisinin to 500 mg mefloquine increased the efficacy and reduced the rate of recrudescence, but this regimen was not adequate and, for short course regimens, more doses of artemisinin as well as higher doses of mefloquine should be studied.

Keywords: malaria, *Plasmodium falciparum*, chemotherapy, artemisinin, mefloquine, Viet Nam

Introduction

Resistance of *Plasmodium falciparum* to 4-aminoquinolines and sulfadoxine–pyrimethamine is widespread in Viet Nam. Quinine resistance has not been documented unequivocally but treatment with quinine has substantial side effects and there is poor compliance with the lengthy, therapeutic course.

New, effective therapeutic regimens which are easy to comply with are needed. Early treatment is important to prevent the progress of disease and to reduce mortality. Mefloquine was available in Viet Nam to a limited extent; the price precluded its use in rural areas. Fears existed about its toxicity and side effects, especially vomiting at higher dose, and there was very little information on its efficacy.

In a double-‘blind’ study low dose mefloquine (10 mg/kg) resulted in 100% clinical cure of 80 adults and 40 children with malaria (ANH *et al.*, 1990). This dose was as effective as a higher dose of 15–20 mg/kg in children. However, patients were followed for only 7 d, not till day 28. Artemisinin (qinghaosu) and derivatives have proved to be very effective antimalarial drugs without significant side effects but monotherapy results in recrudescences in a large proportion of patients. Longer duration of therapy reduces this rate but is in conflict with good compliance. Thus the combination of an artemisinin drug that gives fast initial parasite killing with another drug that prevents recrudescence is a logical step. This strategy may also limit the development of resistance to artemisinin and the combination drug.

The combination of artemisinin with low dose mefloquine was used to some extent in 1992 in the south of Viet Nam. Thus we decided to study whether this combination was more effective than mefloquine alone and to see if any of these regimens could be advocated in the countryside, where they were already tentatively employed.

Patients and Methods

The study was carried out from February 1993 until September 1994 at the hospital in Duc Linh District, Binh Thuan Province, in the south of Viet Nam. The

district is a so-called new economic area, with land recently made available for cultivation. This lowland area is mainly inhabited by people who moved in from areas non-endemic for malaria. The population in the surrounding forest mountains has some degree of immunity against malaria because of the more intense transmission.

Patients older than 8 years with uncomplicated falciparum malaria and parasitaemia between 1000 and 100 000/μL (0.025–2.5%) were included in the study if they or their guardians gave informed consent. Complicated malaria, pregnancy, lactation, mixed infections, inability to take oral medication, and previous participation in the study were criteria for exclusion, as were known allergy to one of the compounds and intake of quinine in the previous 12 h, of artemisinin or derivatives in the previous 24 h, or of mefloquine, tetracycline or doxycycline during the last 7 d. Use of chloroquine and sulfadoxine–pyrimethamine were not regarded as a reason for exclusion because of widespread resistance to these drugs.

The study was a randomized, double-‘blind’ comparison between a regimen of 500 mg artemisinin (produced by ACF-Chemie, Maarssen, The Netherlands, from Vietnamese artemisinin) followed 2 h later by mefloquine (Mephaquine™; Mepha, Switzerland) (combination therapy) and a regimen of placebo followed 2 h later by mefloquine. Mefloquine was given at 500 mg for patients with a body weight over 37.5 kg, and 375 mg for patients of less weight.

Based on the few available data of efficacy and an expected number of 20 drop-outs per group, it was estimated that 120 patients were needed in each group ($\alpha=0.05$, $\beta=0.8$). Patients were admitted to hospital, physical examination was performed every day and symptoms were recorded. Vital signs were recorded every 8 h until at least 3 normal readings of temperature ($\leq 37^\circ\text{C}$ axillary) were obtained.

Fever and parasite clearance times were defined as the time from drug administration to the first of 3 consecutive normal temperature readings and the first of 3 negative blood slides, respectively. Thick and thin blood films were prepared every 8 h. Patients were discharged from hospital after fever and parasite clearance, and then blood films were prepared on an out-patient basis 7, 14, 21 and 28 d after the start of therapy. Blood films were examined at the study site and reviewed at Cho

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Ray Hospital, Ho Chi Minh City. Parasite density was expressed as the number of parasites per μL , estimated from the number of parasites per leucocyte in a thick blood film multiplied by the white blood cell count per μL . Clinical and parasitological outcome were assessed separately. Clinical failure was defined as no clinical improvement, necessitating additional treatment within the first 48 h of treatment (early failure) or after 48 h of therapy (late failure).

Parasitological response was defined as follows. Radical cure: parasite clearance by day 7 without recrudescence up to day 28; RI: disappearance of parasites with no asexual parasite detected at day 7 but recrudescence before day 14 (early RI) or on days 14–28 (late RI); RII: marked reduction of the parasite count to <25% of the initial value, without clearance by day 7; RIII: no response or only a small decrease of parasitaemia to not less than 25% of the initial value assessed 48 h after therapy. In cases of clinical failure, therapy consisted of intravenous artesunate and oral mefloquine; in cases of recrudescence, the local standard treatment was given (artemisinin–mefloquine or quinine).

A symptom was regarded as a drug-related side effect if it occurred after initiation of therapy or, if already present before the first dose, increased in intensity thereafter. Data were entered into the computer program Epi-Info (version 5.01 b, July 1991; Centers for Disease Control and Prevention, Atlanta, Georgia, USA). Student's *t* test, the Kruskal–Wallis and χ^2 tests were performed with this package and with Statview® on an Apple Mackintosh computer. Cox's regression analysis of the cumulative fever, parasite clearance and recrudescence was performed with KMSURV® (Ludwig Institute for Cancer Research, São Paulo, Brazil). Statistical significance was taken as $P < 0.05$. No interim analysis was scheduled beforehand.

All patients were informed about the study and oral consent was obtained. The study protocol was approved by the medical ethics committee of the Academic Medical Centre, Amsterdam, The Netherlands, and institutional clearance was obtained from Cho Ray Hospital, Viet Nam.

Results

Two hundred and forty patients participated in the study (122 receiving combination therapy, 118 mefloquine only). On review of the slides, 9 patients (5 combination, 4 mefloquine) appeared to have been wrongly included because they had *P. vivax* infections ($n=8$) or gametocytes only ($n=1$). Three cases who had an initial parasite count $>100\,000/\mu\text{L}$ and 2 children who appeared to be 6 years old had been wrongly entered but were not excluded. The demographic characteristics of the 231 included patients, some base-line values and the dosages per kg body weight, are shown in Table 1.

There was no significant difference between the groups with respect to these quantities. The outcome is shown in Table 2.

One combination therapy patient left the hospital before any end-point had been reached. In both groups there was one early clinical failure. The combination therapy failure, who had an initial parasite count of $80\,000/\mu\text{L}$, deteriorated clinically, not parasitologically, and was given intravenous artesunate 24 h after starting therapy. Thereafter he recovered. The mefloquine patient, who had an initial parasite count of $100\,000/\mu\text{L}$, developed signs of cerebral malaria, concurrent with an increase of the parasite count to $200\,000/\text{mL}$. Intravenous artesunate was administered 28 h after the mefloquine dose, but the patient died in respiratory failure on the way to a referral hospital. One patient in the mefloquine group was given artesunate at 48 h because of an RIII parasitological response. He quickly responded. Another patient (also on mefloquine) developed signs of respiratory failure at 48 h, when parasitaemia had disappeared. She was referred for supportive treatment and recovered.

Parasitological results, parasite clearance times for the patients who recovered without additional treatment (excluding the RII cases), and fever clearance times are shown in Table 2. The mean parasite clearance time was 15 h (SD=7) for patients receiving combination therapy and 25 h (SD=18) for recipients of mefloquine only ($P < 0.0001$). The corresponding mean 95% parasite clearance times were 22 h (SD=9) and 40 h (SD=25) ($P < 0.0001$).

There was a weak positive correlation between baseline parasitaemia and parasite clearance time in both groups ($r=0.374$, $P=0.0001$ for combination therapy and $r=0.924$, $P=0.016$ for mefloquine alone). No other association between baseline parasitaemia and outcome was found. Cox's regression analysis of the cumulative proportion of parasitaemic patients showed that those patients receiving combination therapy cleared parasites faster than those receiving mefloquine alone ($P < 0.0001$).

The parasite clearance time in the combination therapy group was similar in patients with different parasitological outcomes. In the mefloquine group, the mean parasite clearance time was 53 h (SD=25) for radically cured patients, 87 h (SD=26) for patients with early recrudescences ($P < 0.05$ compared with radical cure) and 68 h (SD=20) for patients with late recrudescences ($P < 0.05$ compared to radical cure and also to early recrudescence). The parasitological outcome and parasite clearance time were not related to the mean dose per kg body weight of artemisinin and/or mefloquine in either group. The recrudescence rate shown in Table 2 was calculated for patients who were followed up to 28 d after starting therapy (the difference was significant,

Table 1. Characteristics of 231 patients with uncomplicated falciparum malaria treated with two different regimens in the south of Viet Nam

	Treatment regimen ^a	
	Artemisinin plus mefloquine ^b	Mefloquine ^c
No. of subjects	117	114
Sex (male/female)	106/11	97/17
Age (years)	25±8 (6–50)	26±8 (6–59)
Weight (kg)	47±9 (16–61)	46±8 (17–61)
Body temperature on admission (°C)	38.9±1.1 (37.5–39.4)	38.9±1.0 (37.5–41.4)
Initial parasitaemia (μL)	2715±47226 (1000–437500)	24565±21267 (1000–100000)
Baseline gametocyte prevalence ^d	30% (35/116)	30% (34/113)
Artemisinin dose (mg/kg)	11.5±4.1 (8.2–32.3)	Nil (placebo)
Mefloquine dose (mg/kg)	10.9±2.4 (8.2–24.2)	10.9±2.0 (8.2–22.1)

^aData are expressed as mean±SD (range in parentheses), except gametocyte prevalence. There was no significant difference between the 2 groups.

^bTwo capsules of 250 mg artemisinin each plus 2 tablets of 250 mg mefloquine each.

^cTwo tablets of 250 mg mefloquine each.

^dPercentage of subjects with gametocytaemia.

Table 2. Outcome of two treatment regimens for uncomplicated falciparum malaria

	Regimen		Total
	Artemisinin plus mefloquine ^a	Mefloquine ^b	
No. of subjects	117	114	231
Not evaluable (early drop-out)	1	—	1
Failure			
Early	1	1	2
Late	—	2 ^c	2
Lost before day 7 ^d	1	1	2
Lost days 7–28 ^e	—	1	1
Resistant (RII)	—	3 ^c	3
Recrudescence			
Early	7	15	22
Late	10	17	27
Rate ^f	15%	30%	21%
Radical cure	97	74	171
Parasite clearance time (h) ^g	40±16 (8–112)	60±28 (8–144)	—
Fever clearance time (h) ^h	22±14 (0–64)	31±27 (0–120)	—

^aTwo capsules of 250 mg artemisinin each plus 2 tablets of 250 mg mefloquine each.

^bTwo tablets of 250 mg mefloquine each.

^cSee text for details.

^dLost for evaluation of radical cure or recrudescence, after initial recovery and parasite clearance.

^eLost for calculation of recrudescence rate but included in logistic regression analysis.

^fEvaluated in 114, 106 and 220 subjects, respectively. The difference between regimens was significant ($P=0.01$, Kruskal-Wallis test).

^gMean ±SD (range in parentheses); evaluated in 113 and 100 subjects, respectively. The difference between regimens was significant ($P<0.0001$, Kruskal-Wallis test).

^hMean±SD (range in parentheses; 0 indicates absence of fever on admission); evaluated in 117 and 114 subjects, respectively. The difference between regimens was significant ($P=0.0015$, Kruskal-Wallis test).

$P=0.01$). Assuming 'best and worst scenarios' (classifying the drop-outs as cured, or as having recrudescences, respectively) gave comparable results ($P=0.01$ for both). The radical cure rate was calculated as a proportion of all included patients: 97/116=84% for combination therapy (excluding the single non-evaluable patient) and 74/114=65% for mefloquine alone ($P=0.002$). If the denominator was calculated on an 'intention to treat' basis, the absolute percentages of radical cure were slightly smaller than when only patients who were followed for 28 d were included. Analysis of proportional cumulative recrudescences, including patients who were lost from follow-up between days 7 and 28, revealed a significant difference between the 2 treatment regimens in favour of the combination treatment ($P=0.006$).

Gametocytes were detected at the initial examination—i.e., before or during the first 24 h after the artemisinin/placebo dose in 30% of the patients in both groups (Table 1). No difference in the rate of disappearance of gametocytes was noted between the 2 groups. Gametocytes were more frequently detected during the out-patient follow-up period in patients who already had gametocytes at the initial examination. Two of 80 combination patients and 14 of 75 receiving mefloquine only, who had no gametocytes initially, developed gametocytaemia at some time during follow-up (relative risk, combination vs. mefloquine, was 0.11 [95% confidence interval 0.02–0.50, $P=0.003$]). In the mefloquine only group, gametocytes were significantly more often present in patients with early recrudescences than in radically cured patients or patients with late recrudescence. This effect was not seen in the combination group.

Vomiting occurred in one patient during combination treatment, and in none of those receiving mefloquine alone. A second dose of mefloquine was tolerated well. No other side effect was noted.

Discussion

The study showed that a low single dose of mefloquine (c. 10 mg/kg body weight) was followed by a high rate of recrudescence (30%) and was therefore not adequate for the treatment of uncomplicated falciparum

malaria in the south of Viet Nam. The addition of a single dose of artemisinin resulted in faster disappearance of parasites, quicker defervescence, and a lower recrudescence rate but a recrudescence rate of 15% is also not acceptable. Reinfection and recrudescence could not be differentiated; how great is the chance of reinfection in the area is not known, but it is presumably small. Some of the recrudescences in both groups could have been due to reinfection, and the performance of the combination treatment might therefore have been slightly better than presented. The predominance of male patients suggested that infection occurred outdoors. Men often worked in the forests where they stayed overnight without the protection of bed nets.

No side effect was documented except for occasional vomiting. The intake of the medication gave no problem and, since this regimen can be applied while observing the patient for a short period, the combination of artemisinin with mefloquine seems to be very suitable for out-patient treatment.

The effective dose of artemisinin has been determined empirically. The limited pharmacokinetic data available indicate that, after an oral dose of 500 mg, plasma concentrations are above the minimum inhibitory concentration for 12 h (DUC *et al.*, 1994). Whether the dose in combination with mefloquine should be the same as that used in monotherapy is not completely clear. Clinical studies in China used higher dosages of artemisinin and mefloquine than in the present study, but the sample sizes were small and no real dose-finding was done (JIANG *et al.*, 1982; LI *et al.*, 1984).

Combinations of other artemisinin derivatives with mefloquine have been shown to be effective in the treatment of uncomplicated falciparum malaria in Thailand (LOOAREESUWAN *et al.*, 1992; BUNNAG *et al.*, 1995; KARBWANG *et al.*, 1995). Suitable doses of artemisinin cannot, however, be inferred from these studies on its derivatives.

The recommended dose of mefloquine as monotherapy is 15 mg/kg body weight (WHO, 1990) but in Thailand higher dosages are needed. The optimal dose in combination with artemisinin and derivatives has not yet been defined. There are suggestions that, in combinations of artesunate or artemether with mefloquine,

plasma concentrations of mefloquine are lower than with monotherapy (KARBWANG *et al.*, 1994, 1995). Clinical studies comparing the efficacy of low (15 mg/kg) and high (25 mg/kg) doses of mefloquine in combination with artemether in Thailand were not conclusive (BUNNAG *et al.*, 1995; KARBWANG *et al.*, 1995). The results of the present study cannot readily be compared to results from Thailand. In Thailand, mefloquine resistance has evolved quickly since the drug was introduced (NOSTEN *et al.*, 1991; WONGSRICHANALAI *et al.*, 1992). The present study started at a time when artemisinin and mefloquine were not readily available in Duc Linh. At that time, the prevalent malaria parasites could be regarded as naive with respect to exposure to the 2 drugs and throughout the duration of the study the response to therapy did not change.

The artemisinin-mefloquine combination was more effective than mefloquine alone for initial parasite killing. This is in agreement with previous studies, all showing that artemisinin and derivatives are fast acting compounds. The difference in recrudescence rate between our 2 groups of patients showed that this rapid initial parasite killing had some protective effect against recrudescence. The difference may be a reflection of the chance that a parasite survives long enough to initiate a recrudescence, a chance that is smaller when the parasite burden is eliminated more efficiently. Similarly, the difference in the prevalence of gametocytaemia during follow-up can be explained. No effect on the gametocytes was detected initially, but the rapid elimination of parasites by artemisinin decreases the chance of gametocytes developing later. A direct effect of artemisinin on gametocytes, reported by KUMAR & ZHENG (1990) and DUTTA *et al.* (1990), could not be confirmed in this study.

In conclusion, a single 500 mg dose of artemisinin (10 mg/kg) added to a single 500 mg dose of mefloquine (10 mg/kg) is effective for initial parasite killing and reduces the recrudescence rate in uncomplicated falciparum malaria, as well as gametocyte development. Longer therapy with artemisinin and a higher dose of mefloquine will be needed to prevent recrudescence and thus the risk of selection of resistant strains of *P. falciparum*.

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