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

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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 100000µL (0.025–2.5%) were included in the study if they or their guardians gave informed consent. Compli- cated 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 deriv- atives 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, Maarsen, 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 (α=0.05, β=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 (≤37°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 thin 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...
Table 1. Characteristics of 231 patients with uncomplicated falciparum malaria treated with two different regimens in the south of Viet Nam.

<table>
<thead>
<tr>
<th>Treatment regimena</th>
<th>Artemisinin plus mefloquineb</th>
<th>Mefloquinec</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>117</td>
<td>114</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>106/11</td>
<td>97/17</td>
</tr>
<tr>
<td>Age (years)</td>
<td>25±8.6 (6-50)</td>
<td>26±8.6 (6-59)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>47±9.16 (16-61)</td>
<td>46±8.17 (17-61)</td>
</tr>
<tr>
<td>Body temperature on admission (°C)</td>
<td>38.9±1.1 (37.5-39.4)</td>
<td>38.9±1.0 (37.5-41.4)</td>
</tr>
<tr>
<td>Initial parasitaemia (μL)</td>
<td>2715±4722 (1000 437500)</td>
<td>2456±921 (1000 100000)</td>
</tr>
<tr>
<td>Baseline gametocyte prevalenced</td>
<td>35% (34/116)</td>
<td>30% (34/113)</td>
</tr>
<tr>
<td>Artemisinin dose (mg/kg)</td>
<td>11.5±4.1 (8.2-32.3)</td>
<td>Nil (placebo)</td>
</tr>
<tr>
<td>Mefloquine dose (μg/kg)</td>
<td>10.9±2.4 (8.2-22.4)</td>
<td>10.9±2.0 (8.2-22.1)</td>
</tr>
</tbody>
</table>

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

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 800000 μL, 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 1000000 μL, developed signs of cerebral malaria, concurrent with an increase of the parasite count to 2000000 μL. 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=15) for recipients of mefloquine alone (P<0.001). 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=0.248, 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<0.001).

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=35) 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 2. Outcome of two treatment regimens for uncomplicated falciparum malaria

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of subjects</th>
<th>Not evaluable (early drop-out)</th>
<th>Failure</th>
<th>Late</th>
<th>Lost before day 7th</th>
<th>Lost days 7–28</th>
<th>Resistant (RI)</th>
<th>Recrudescence</th>
<th>Parasite clearance time (h)</th>
<th>Fever clearance time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemisinin plus mefloquine</td>
<td>117</td>
<td>1</td>
<td>Early</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>40±16 (8-112)</td>
<td>22±14 (0-64)</td>
<td></td>
</tr>
<tr>
<td>Mefloquine</td>
<td>114</td>
<td>2</td>
<td>Late</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>60±28 (8-144)</td>
<td>31±27 (0-120)</td>
<td></td>
</tr>
</tbody>
</table>

| | Total | | | | | | | | | |
| Artemisinin plus mefloquine | 231 | 1 | Early | 2 | 2 | 2 | 3 | 40±16 (8-112) | 22±14 (0-64) |
| Mefloquine | 21 | | Late | 2 | 2 | 2 | 3 | 60±28 (8-144) | 31±27 (0-120) |

a Two capsules of 250 mg artemisinin each plus 2 tablets of 250 mg mefloquine each.
b Two tablets of 250 mg mefloquine each.

c See text for details.
d Lost for evaluation of radical cure or recrudescence, after initial recovery and parasite clearance.
e Lost for calculation of recrudescence rate but included in logistic regression analysis.
f Evaluated in 114, 106 and 220 subjects, respectively. The difference between regimens was significant (P=0.01, Kruskal–Wallis test).
g Mean ± SD (range in parentheses); evaluated in 113 and 100 subjects, respectively. The difference between regimens was significant (P=0.001, Kruskal–Wallis test).
h Mean ± 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 50% 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 had 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 (JUC 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 (LOOARESUWAN et al., 1992; BUNNAG et al., 1995; KARUPWANG et al., 1995). Suitable dosages 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 is still not been defined. There are suggestions that, in combinations of artesunate or artemether with mefloquine,
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**References**


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