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 \((p=0.001)\). 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 \((\text{Anht et al.}, 1990)\). 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 \((\text{qinghaosu})\) 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 \((\text{produced by ACF-Chemie, Maarsen, The Netherlands, from Vietnamese artemisinin})\) followed 2 h later by mefloquine \((\text{Mephaquine®; Mepha, Switzerland})\) \((\text{combination therapy})\) 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 \((a=0.05, \beta=0.8)\). 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 \((<37°C \text{ axillary})\) 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...
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 $\geq 100,000/\mu L$ 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 baseline values and the parasitological outcome were obtained from Cho Ray Hospital, HCM City.

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 80100(0) $\mu L$, 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 100000 $\mu L$, developed signs of cerebral malaria, concurrent with an increase of the parasite count to 200000 $\mu L$. Intravenous artesunate was administered 26 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 RI/II 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 RI/II 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 41 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 fever proportion of parasitaemic patients showed that those patients receiving combination therapy cleared parasitaemia 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=29) for radically cured patients, 87 h (SD=26) for patients with early recrudescences (P<0.05 compared to 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 days 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 Vietnam

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>No. of subjects</th>
<th>Sex (male/female)</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Body temperature on admission (°C)</th>
<th>Initial parasitaemia (μL)</th>
<th>Baseline gametocyte prevalence</th>
<th>Artemisinin dose (mg/kg)</th>
<th>Mefloquine dose (μg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemisinin plus mefloquine</td>
<td>117</td>
<td>106/11</td>
<td>252.8 (6-50)</td>
<td>475.9 (16-61)</td>
<td>38.92-11.1 (37.5-39.4)</td>
<td>2715 ± 47226 (1000 437500)</td>
<td>2456 ± 21367 (1000 100000)</td>
<td>11.5 ± 0.0 (8.2-12.3)</td>
<td>11.9 ± 0.9 (8.2-24.2)</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>114</td>
<td>97/17</td>
<td>263.8 (6-59)</td>
<td>462.8 (17-61)</td>
<td>38.92-11.0 (37.5-41.4)</td>
<td>2456 ± 21367 (1000 100000)</td>
<td>30% (34/116)</td>
<td>Nil (placebo)</td>
<td>10.9 ± 2.0 (8.2-22.1)</td>
</tr>
</tbody>
</table>

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

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

$c$Two tablets of 250 mg mefloquine each.

$d$Percentage of subjects with gametocytaemia.
Table 2. Outcome of two treatment regimens for uncomplicated falciparum malaria

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Parasite clearance time (h)</th>
<th>Fever clearance time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40±16 (8; 112)</td>
<td>60±28 (8; 144)</td>
</tr>
<tr>
<td>Total</td>
<td>22±14 (0-64)</td>
<td>31±27 (0-120)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Radically cured</th>
<th>Recrudesce</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td></td>
<td>22%</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td>17%</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td>15%</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>97%</td>
<td>74%</td>
</tr>
</tbody>
</table>

*Numbers in parentheses indicate ranges.*

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 artesunate resulted in faster disappearance of parasites, quicker defervescence, and a lower recrudescence rate but a recrudescence rate of 13% is also not acceptable. Re-infection and recrudescence could not be differentiated; how great is the chance of re-infection in the area is not known, but it is presumably small. Some of the recrudescences in both groups could have been delayed due to rebound, 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 artesunate with mefloquine seems to be very suitable for outpatient treatment.

The effective dose of artesunate 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 concentrations for 12 h (JUC et al., 1999). 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 artesunate and mefloquine than in the present study, but the sample sizes were small and no real dose-finding was done (JANG et al., 1982; LI et al., 1984).

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

The recommended dose of mefloquine as monotherapy is 15 mg/kg body weight (WHO, 1996) but in Thailand higher dosages are needed. The optimal dose in combination with artesunate and derivatives is still not 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 artesunate 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 artesunate 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 artesunate–mefloquine combination was more effective than mefloquine alone for initial parasite killing. This is in agreement with previous studies, all showing that artesunate 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 by artesunate decreases the chance of 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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References


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