# ARTEMETHER IN THE TREATMENT OF MULTIPLE DRUG RESISTANT FALCIPARUM MALARIA

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**Abstract.** Artemether has the potential to be an alternative antimalarial for multiple drug resistant falciparum malaria. However, it has been associated with high recrudescent rates which may be due to incorrect dosage regimens. The dosage regimens are varied from country to country. We have carried out a comparative study of two dosage regimens, *ie* 480 mg and 600 mg total dose given over 5 days in uncomplicated and severe falciparum malaria. 167 patients were included in the study, 61 with acute uncomplicated falciparum malaria and 106 with severe malaria. All patients showed a good initial response. The difference in total dose had no effect on the parasite or fever clearance time (PCT or FCT). However, the severity of the disease did have some influence of these times. The PCT and FCT from either regimen of uncomplicated malaria were significantly faster than those of severe malaria ($p < 0.005$ and $= 0.05$, respectively). The cure rate seems to have some correlation with the amount of drug given and severity of the disease. The cure rates in uncomplicated malaria were 84 and 92%, respectively, for 480 mg and 600 mg. In severe malaria the cure rates dropped to 65 and 76%, respectively, for 480 and 600 mg. We conclude that artemether can be considered as an alternative antimalarial for multiple drug resistant falciparum malaria. However, the cure rate of severe falciparum malaria in this study is not considered satisfactory in areas with multiple drug resistant falciparum malaria. Further studies are needed to assess the curative efficacy with different dosage regimens. The dose in severe malaria is likely to be higher than that in uncomplicated malaria.

## INTRODUCTION

Artemether has been shown to be a very potent antimalarial. It is active against severe falciparum malaria in the Republic of China and Myanmar (Burma) with a faster reduction of parasitemia than other antimalarial drugs (Li *et al* 1982; China Cooperative Research Group on Qinghaosu 1982; Wang and Xu, 1985; Pe Than Myint and Tin Shwe, 1987). It is valuable in severe falciparum malaria as the aim of the treatment is to reduce the parasite burden rapidly. However, artemether has been shown to be associated with high recrudescent rates, particulary in severe malaria (Pe Than Myint and Tin Shwe, 1986; 1987; Bunnag *et al,* 1990). The proper dosage regimen has not yet been established in areas with high multiple drug resistance. In Thailand, there is increasing resistance of strains of *P. falciparum* to available antimalarial drugs and these resistant strains are rapidly spreading (Karbwang and Harinasuta, 1992). Alternative drugs with cure rates approaching 100% are highly desirable.

## MATERIALS AND METHODS

The study was carried out in the Bangkok Hospital for Tropical Diseases where malaria transmission is not possible, thus reinfection could be excluded. The study was done during 1989-1990. Febrile male patients with positive asexual forms of *P. falciparum* in their peripheral blood, with no history of previous antimalarials for this episode of illness, aged between 15-45 years old and weight 45-60 kg, were recruited into the study. The patients were included in group A if they had parasite counts less than 200,000/μl with no sign of severe malaria as defined by WHO (1990). The patients were included in group B if they had severe malaria. The study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University. Written informed consent to participate in the study was obtained from all patients.

Two dosage regimens of daily intramuscular artemether for 5 days were randomly given to

patients in groups A and B. The regimens was either artemether (Arthermin®) 480 mg total dose given an 160 mg initial dose followed by 80 mg daily for another 4 days, or 600 mg total dose given as 200 mg initial dose followed by 100 mg daily for another 4 days.

Prior to treatment (day 0) blood samples were taken for complete blood count, biochemistry, quantitative parasite count. Parasite count was performed every 6 hours until negative (thick and thin film) then daily until day 28. Complete blood count and biochemistry were monitored on days 2, 4, 7 and then weekly until day 28. Vital signs were recorded every 6 hours. Clinical observation was evaluated on admission and daily for 28 days.

*In vitro* sensitivity tests for chloroquine, quinine, quinidine and mefloquine were performed in all patients on admission, using a microtechnique (Rieckmann *et al,* 1978).

Fever clearance time (FCT) was the time taken for the temperature to fall below 37.5°C and remain at that value for 72 hours. Parasite clearance time (PCT) was the time for the parasite count to fall below the level of microscopic detection (thick film).

The therapeutic response and side effects were evaluated between dosage regimens in each group (A and B) and between groups. The patients were included for efficacy assessment when they had completed the 28 day study period. The response was evaluated according to WHO criteria of S (cure), RI, RII, RIII (WHO, 1973). The adverse-effects, PCT and FCT were evaluated in all patients.

Patients who failed to respond to treatment were treated with quinine sulphate 600 mg three times daily together with tetracycline 250 mg four times daily for 7 days. Patients with vivax malaria during the course of follow-up were treated with chloroquine 150 mg (base) to suppress the symptoms during 28 days of follow-up, then a full course treatment of vivax malaria was given on discharge.

Comparison of normally distributed data was by Student's *t* test. Wilcoxon Rank Sum test was applied if data were not normally distributed. Parasite counts were compared after logarithmic transformation and clearance times were calculated from normalised values. Proportional data were compared by Chi-square test with Yates' correction (cure rate, side effects).

## RESULTS

167 patients were included in the study; 61 with acute uncomplicated falciparum malaria and 106 with severe falciparum malaria. The age and weight of the patients were comparable in both groups (Table 1). No patients had antimalarials prior to admission based on urine screening tests for sulfadoxine and chloroquine and whole blood concentrations of mefloquine.

**Group A:** Admission clinical and laboratory data including parasitemia of patients with uncomplicated malaria in either regimen (480 mg or 600 mg) were comparable (Table 1). Five patients did not complete the 28 day study period. Thus, the efficacy was evaluated in 56 patients, 32 on the 480 mg dosage regimen and 24 on the 600 mg regimen. All patients showed a good initial response with PCT of 34.7 and 34.4 hours, and FCT of 38.4 and 33.5 hours, for 480 mg and 600 mg artemether, respectively. The PCT and FCT were not statistically different between the two regimens. The cure rates were 84% and 92%, for 480 mg and 600 mg regimens, respectively.

**Group B:** Admission clinical and laboratory data including parasitemia of patients with severe malaria in either regimens were comparable (Table 1). All patients showed a good initial response to treatment with PCT of 49.4 and 49.4 hours and FCT of 46.8 and 45.6 hours for 480 and 600 mg regimens, respectively. There was no significant difference between the two regimens regarding PCT and FCT. Ten patients (7 with 480 mg and 3 with 600 mg) did not complete the 28 day study period. Therefore, the efficacy was based on 96 patients (46 in the 480 mg regimen and 50 in the 600 mg regimen). The cure rates were 65% and 76%, for 480 and 600 mg regimens, respectively. One patient with coma and one with drowsiness on admission recovered rapidly with no sequelae.

The PCT and FCT of patients in group A with either regimen were significantly faster than those of group B (Table 2). The mean parasite clearance curves for group A and B are presented in Fig 1. The cure rate in the 480 mg regimen tended to be

Table 1

Clinical and laboratory data on admission.

| | Uncomplicated malaria | | Severe malaria | |
|---|---|---|---|---|
| | 480 mg | 600 mg | 480 mg | 600 mg |
| Mean (SD) | | | | |
| Age (year) | 23 (9) | 22 (5) | 26 (8) | 28 (10) |
| Weight (kg) | 49.8 (10.1) | 53.9 (6.4) | 53.5 (8.1) | 55.4 (8.5) |
| Temperature (°C) | 38.7 (0.6) | 38.5 (0.6) | 38.4 (0.8) | 38.4 (0.9) |
| PCV (%) | 35.4 (7.6) | 36.7 (7.0) | 36.2 (7.1) | 37.5 (6.6) |
| Geometic mean (range) Parasite (per μl) | 16,982 (1,332-101,830) | 18,197 (4,880-172,420) | 55,462 (3,800-359,100) | 72,444 (1,725-93,2474) |
| No. of cases | | | | |
| Jaundice | - | - | 18 | 23 |
| Creatinine > 3 | - | - | 23 | 21 |
| Drowsiness | - | - | 1 | - |
| Coma | - | - | - | - |

Table 2

Response of treatment.

| | Uncomplicated malaria | | Severe malaria | |
|---|---|---|---|---|
| | 480 mg N = 33 | 600 mg N = 28 | 480 mg N = 53 | 600 mg N = 53 |
| Mean (range) | | | | |
| PCT (hours) | 34.7 (18-60)[a] | 34.4 (24-60)[c] | 49.4 (18-104) | 49.4 (18-125) |
| FCT (hours) | 38.4 ( 2-158)[b] | 33.5 (12-108)[d] | 46.8 (15-177) | 45.6 ( 9-132) |
| No. patients (%) | | | | |
| S | | | 30 (65) | 38 (76) |
| RI | 27 (84) | 22 (91.7) | 16 (35) | 12 (24) |
| RII | 5 (16) | 2 (8.3) | - | - |
| RIII | - | - | - | - |
| S/RI (follow-up < 28d) | - | - | 7 | 3 |
| *P. vivax* | 1 | 4 | 5 (11) | 13 (26) |
| | 2 (6) | 5 (22) | | |

a = Significantly faster than PCT of severe malaria with 480 mg regimen (p = 0.000008)
b = Significantly faster than FCT of severe malaria with 480 mg regimen (p = 0.046)
c = Significantly faster than PCT of severe malaria with 600 mg regimen (p = 0.009)
d = Significantly faster than FCT of severe malaria with 600 mg regimen (p = 0.001)

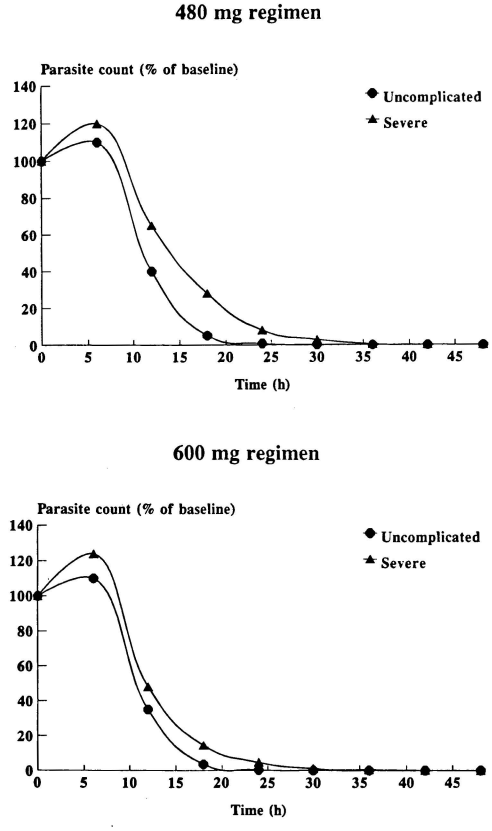


Fig 1—Mean parasite clearance curve.

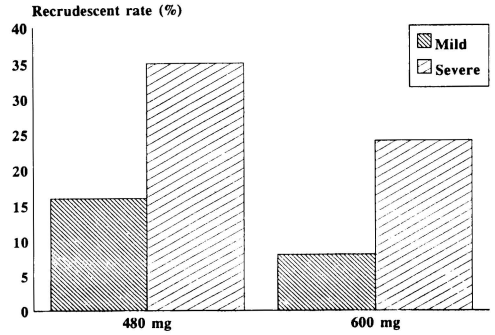


Fig 2—Recrudescent rate in uncomplicated and severe malaria.

lower than that of the 600 mg regimen in either group, although they were not statistically different due to small sample size. Either regimen in group A showed a trend of having a lower recrudescent rate than group B (Fig 2).

Side-effects were mild and transient. The occurrence of side-effects in either group was similar in both regimens (Table 3). There were no drug associated biochemical and blood profile changes during hospitalization. Vivax malaria was found during the follow-up period in both groups with either regimen from day 14 to 28 (Table 2).

*In vitro* MIC (minimum inhibitory concentration) of chloroquine, quinine, quinidine and mefloquine are shown in Table 4. The MIC of all tested drugs confirmed the existence of multiple drug resistant falciparum strains.

## DISCUSSION

Multiple drug resistant falciparum malaria in Thailand is rapidly spreading. Mefloquine, the first-line drug for falciparum malaria is no longer effective in the eastern part of Thailand. The cure rate for mefloquine at the conventional dose (750 mg) was only 30%; increasing the dose to 1,250 mg has increased the cure rate to 76% (Karbwang and Harinasuta, 1992). However, the mefloquine resistance has developed rapidly with an increase in RII response (Karbwang and Harinasuta, 1992). This high grade of resistance will soon prevent the use of mefloquine in such areas. Alternative drugs are urgently needed.

Artemether at a total dose of 480 mg or 600 mg in either uncomplicated or severe malaria was well tolerated. The initial response was excellent in all patients. The FCT and PCT were rapid in uncomplicated malaria. The use of artemether is clearly important in uncomplicated malaria because of its rapid clearing of the parasites which results in preventing the further development of young trophozoites and thus reduces the risk of cerebral or severe malaria. The PCT and FCT were found to be longer in severe malaria than uncomplicated malaria in our study, in agreement with a recent study in Gambian children (White *et al,* 1992). It is likely that there were more sequestered parasites in severe malaria. Artemether acts mainly on the early ring forms. It may not be as active with larger ring, late trophozoites or schizonts that are seque-

Table 3

Side effects.

| | Uncomplicated malaria | | Severe malaria | |
|---|---|---|---|---|
| | 480 mg N = 33 | 600 mg N = 28 | 400 mg N = 53 | 600 mg N = 53 |
| No. patients (%) | | | | |
| Dizziness | 1 (3) | 3 (11) | 7 (13) | 6 (11) |
| Nausea | 1 (3) | - | 4 (8) | 2 (4) |
| Vomiting | 1 (3) | 3 (11) | 7 (13) | 5 (9) |
| Diarrhea | 2 (6) | 2 (7) | 3 (6) | 4 (8) |

Table 4

*In vitro* sensitivity of antimalarial drugs.

| | Chloroquine μM | Quinine μM | Quinidine μM | Mefloquine μM |
|---|---|---|---|---|
| Uncomplicated malaria | | | | |
| - 480 mg | 0.71 | 3.48 | 0.99 | 0.24 |
| - 600 mg | 0.93 | 4.10 | 0.99 | 0.25 |
| Severe malaria | | | | |
| - 480 mg | 1.33 | 3.54 | 1.43 | 0.36 |
| - 600 mg | 1.33 | 4.99 | 1.40 | 0.33 |

stered in the tissues; however, the activity should be rapid again upon the proliferation of the parasites in the new cycle.

The cure rate seems to have a good correlation with the dose and severity of the disease (Fig 2). Thus, the dosage regimens for patients with different degrees of severity should be different. The effective dosage regimen of artemether is different from area to area. In China, at a dose of 480 mg given over 3 to 4 days the cure rate was above 90%, but the most effective regimen was 600 mg given over 4 days (China Cooperative Research Group on Qinghaosu, 1982). In Myanmar, a total dose of 600 mg given over 3 days gave satisfactory results (Pe Than Myint and Tin Swe, 1986, 1987). Our study showed high recrudescent rates with 480 mg total dose in either uncomplicated or severe malaria, suggesting that the minimum dose for multiple drug resistant malaria must be over 480 mg. The cure rate was higher in either group with 600 mg but in severe malaria the cure rate dropped to 76% which is considered unsatisfactory. It is true that from the individual patient's view point the speed of action is more important than cure rate in severe infection (White and Krishna, 1989); however, in areas where multiple drug resistant strains of falciparum are rapidly spreading, the aim of the treatment should be 100% cure, to prevent further spreading.

Although the cure rate of artemether is not 100% in severe malaria, it is still considered as an effective alternative antimalarial to mefloquine because of its rapid clearing of the parasites and no RII or RIII type of response has yet been noted. However, the dosage regimen must be adjusted. Further studies are therefore needed, to assess the

curative efficacy of artemether which would result in a cure rate approaching 100% in multiple drug resistant falciparum malaria. The dose and duration of treatment are likely to be important in adjusting the regimens for severe malaria. It would be easier if information of pharmacokinetics of artemether in falciparum malaria patients becomes available. With the lack of this information, the adjustment has to be made empirically based on the response of the treatment.

The combination of artemether with other antimalarials should also be considered, particularly with the evidence of synergistic effect of artemisinin and mefloquine, halofantrine or quinine *in vitro* (Chawira *et al,* 1987; Ekong and Warhurst, 1990) and *in vivo* (Tin Shwe *et al,* 1988; 1989). Further studies on the use of these combinations in the treatment of multiple drug resistant falciparum malaria should be explored urgently.

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