DOUBLE BLIND RANDOMISED CLINICAL TRIAL OF TWO DIFFERENT REGIMENS OF ORAL ARTESUNATE IN FALCIPARUM MALARIA

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Abstract. A double blind randomized comparative trial of the efficacy of 7-day and 5-day courses of oral artesunate at 600 mg was studied in 89 Thai patients with uncomplicated falciparum malaria. Eighty patients completed the 28-day follow-up period. Artesunate was found to be well tolerated in either regimen. There was an increase of 7% in the cure rate obtained from a 7-day regimen. In 43 patients with a 7-day regimen, the cure rate was 92.5% and 15 patients showed *P. vivax* in their peripheral blood between days 12 and 34. The mean fever and parasite clearance times were 20 and 40 hours, respectively. In 46 patients with a 5-day regimen, the cure rate was 85% and 8 patients showed *P. vivax* during days 13 and 24. The mean fever and parasite clearance times were 29 and 40 hours, respectively.

Although the cure rates of oral artesunate were high in both regimens, the efficacy was considered unsatisfactory since the aim of the treatment is to achieve 100% cure rate. We suggest however that the extension of the duration of treatment to 7 days together with the increase in total dose may improve therapeutic efficacy of artesunate in falciparum malaria.

INTRODUCTION

Artesunate (qinghaosu derivative) has been shown to be effective against multi-drug resistant falciparum malaria (Bunnag *et al,* 1990; 1991). It has a rapid onset of action and rapidly cleared parasites with virtually no adverse-effects. However, it was shown in our previous study that with a one or a three days course regimen of 600 mg (total dose) the recrudescence rate (RI) was 100% (Bunnag *et al,* 1990). Extending the treatment period to 5 days with a daily or twice daily dose has been shown to improve the cure rate to 72-76% (Bunnag *et al,* 1991). The duration of treatment seems to be a vital factor to successful treatment. However, 5 days of treatment appeared to be inadequate to achieve 100% cure rate. It has been shown in the previous study with quinine that all the patients who had quinine levels higher than the minimum inhibitory concentration (MIC) throughout 7 days corresponded with curative outcome (Chongsuphajaisiddhi *et al,* 1981). We therefore compared the efficacy of artesunate 600 mg given at a duration of 7 days versus 5 days.

MATERIALS AND METHODS

Patients

Eighty-nine falciparum malaria patients with acute uncomplicated malaria (asexual form parasitemia of less than 5%), aged between 14 and 48 years and weight ranged 44 to 65 kg, with no history of liver or kidney disease were recruited into the study. No other drug was given during the study period. Written informed consent to participation in the study was obtained from all patients. The study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

Each patient had physical examination, baseline blood examination (including G6PD and hemoglobin typing), blood chemistry investigations, parasite count and electrocardiogram (ECG). Urine screening tests for sulfonamides and chloroquine were performed. *In vitro* sensitivity of *P. falciparum* to chloroquine, quinine, quinidine and mefloquine was determined on admission using a microtechnique (Rieckmann *et al,* 1978). All pa-

tients were admitted into the Bangkok Hospital for Tropical Diseases for 28 days. The patients were asked to come back to the hospital when they had fever after discharge.

Treatment

The study was a double blind randomied clinical trial of artesunate at two dosage regimens.

Group A. Artesunate 200 mg as an initial dose followed by 100 mg on the following day (day 1), then placebo for 2 days (day 2 and day 3). Re-start the treatment again on day 4 with 100 mg daily for another 3 days. The total dose of artesunate was 600 mg.

Group B. Artesunate 200 mg as an innitial dose followed by 100 mg daily for another 4 days, then placebo for the last 2 days. The total dose was also 600 mg.

The drug was administered with a glass of water under supervision.

Patients who failed to response to treatment were treated with quinine 500 mg base, 8 hourly and tetracycline 250 mg four times a day for 7 days.

Patients with *P. vivax* during the 28-day period were treated with chloroquine 150 mg base for temporary relief and followed by a full therapeutic course with primaquine after day 28.

Parasite count

Parasite counts were performed six hourly until negative, then once daily until day 28.

Adverse effects

All adverse reactions during the study were recorded with the date and time when they occurred and disappeared. The changes included gastro-intestinal, central nervous, cardiovascular, dermatological, hematological systems and other changes possibly attributable to artesunate.

Blood pressure (BP) measurement was performed at 4 hour intervals during the first week then twice daily until day 28.

ECG was performed on days 0, 2, 4, 7 then weekly until day 28.

Biochemistry was done on days 0, 2, 4, 7 then weekly until day 28. White cell count and reticulocyte count were performed daily for 28 days.

Data analysis

The patients were included for efficacy assessment when the patients had completed the 28-day study period. The efficacy and side-effects were compared between two therapeutic regimens. The parameters used in the determination included parasite clearance time (PCT), fever clearance time (FCT), the cure rate and the occurrence of adverse-effects.

RESULTS

Eighty-nine patients with acute uncomplicated falciparum malaria were recruited into the study. Only eighty patients had a complete follow-up (28 days). Sixty-three percent of the patients in group A and 67% in group B came from eastern border of Thailand, where high multi-drug resistant strains of falciparum malaria exist. The age, weight, the region where they had contracted malaria and baseline laboratory investigations on admission were found to be comparable in both groups (Table 1).

Clinical response

All patients had excellent initial response. No RII or RIII were found in either study groups.

Forty-three patients with a 7-day artesunate regimen group had mean FCT and PCT of 20 and 40 hours, respectively. The 95% parasite clearance time was within 24 hours. Three patients had recrudescence on days 20, 21 and 22. Forty patients completed the 28-day follow-up with the cure rate of 92.5%. Fifteen patients showed *P. vivax* in their peripheral blood between day 12 and 34 (Table 2).

Forty-six patients with a 5-day artesunate regimen had mean FCT and PCT of 29 and 40 hours, respectively. The 95% parasite clearance time was also within 24 hours. Five patients had recrudescence during days 17 to 24. One patient came back to the hospital with *P. falciparum* in the peripheral blood on day 34. Forty patients were completed

Table 1

Clinical data on admission (presented as mean ± SD).

	Group A	Group B
Age (years)	24.7 ± 7.1	26.1 ± 7.1
Weight (kg)	53.6 ± 5.5	53.3 ± 5.1
Hematocrit (%)	34.3 ± 6.6	32.8 ± 8.3
WBC (/μl)	5,088 ± 1,541	5,547 ± 1,945
Parasitemia (/μl)	16,837	12,549
(range)	(3,270 – 179,550)	(2,690 – 104,220)
Temp (°C)	38.6 ± 0.8	38.7 ± 0.7
FBA (days)	6.0 ± 5.5	5.9 ± 4.5

FBA = fever before admission

Table 2

Outcome of treatment (presented as mean ± SD).

	Group A	Group B
PCT (hours)	39.7 ± 12.7	39.9 ± 11.6
FCT (hours)	20.4 ± 13.5	28.6 ± 23.8
P. vivax (cases)	15	10
S response (cases)	37 (92.5%)	34 (85%)
RI response (cases)	3 (7.5%)	6 (15%)

the 28-day follow-up with the cure rate of 85%. *P. vivax* infection was found in 8 patients during days 13-24 (Table 2).

There was an increase of 7% in the cure rate obtained from group A regimen, however, this is not statistically significant difference. There was no statistically difference between the two study regimens regarding PCT, FCT, 95% parasite clearance time and the appearance of *P. vivax* during the 28-day follow-up period.

Adverse effects

Artesunate was well tolerated with either regimen. The ECG, blood pressure and pulse rate showed no drug-associated changes. Erythrocyte counts, hematocrit levels, reticulocyte count, liver function test and renal function were within normal limit throughout the study period.

Eight patients in group A had mild and transient adverse-effects as following : one patient had headache on days 0-7, one patient had vomiting on day 3, two had abdominal pain (peptic type) on days 1-14, one had diarrhea on days 0-4, one with dizziness, itching and tinitus during days 0-4.

Four patients in group B had mild and transient adverse-effects as following : one with body ache on days 6-7, one with abdominal pain on days 1-4, one with flatulence on days 2-4 and one patient lost hair of more than 200 hairs/day on days 2-3.

***In vitro* sensitivity test**

Forty-one isolates were successfully cultured and tested for MIC of chloroquine, quinine, quinidine and mefloquine. Based on WHO criteria for *in vitro* sensitivity test, it was evident that all the

Table 3

In vitro sensitivity test for MIC.

	Group A	Group B
Chloroquine (μM)	1.2	1.4
Quinine (μM)	4.3	5.2
Quinidine (μM)	1.8	2.0
Mefloquine (μM)	0.32	0.4

isolates were resistant to chloroquine. The mean MIC for quinine, quinidine and mefloquine were shown to be high in comparison with the previous study (Table 3, Bunnag *et al,* 1987).

DISCUSSION

Artesunate at the total oral dose of 600 mg given over 5 or 7 days was well tolerated. The FCT and PCT were rapid. The initial response was excellent in all patients. Symptoms and parasites disappeared within 3 days after treatment. Very mild and transient adverse-effects were encountered in both regimens.

The recrudescent rates were between 15 and 7% for 5 and 7 day treatments, respectively. The results of the present study confirmed the efficacy of artesunate in the previous studies (Bunnag *et al,* 1990; 1991). There is no doubt that artesunate can clear the parasite faster than other antimalarials (Bunnag *et al,* 1987; Harinasuta *et al,* 1983; 1987). However, the aim of the treatment is to achieve 100% cure rate; the results of this study are thus considered as unsatisfactory. The extension of the duration of treatment to 7 days without increasing the dose may not be the right choice. It was shown in the previous study that artesunate 650 mg given over 5 day period resulted in a 95% cure rate (Bunnag *et al,* 1990). This suggests that it is time to consider the higher dose, however, it is unfortunate that the pharmacokinetic data for this drug are very limited. The adjustment of dosage regimen would be easier with information on pharmacokinetics of this drug. Alternatively, combination of artemisinin with other antimalarials such as mefloquine and quinine has been shown to produce synergistic effects in *in vitro* study (Chawira *et al,* 1987; Ekong *et al,* 1990), may also be considered. However, drug-drug interaction should be studied before the initiation of clinical trials.

It was noticed in the present study that no parasitemia was seen even when the treatment was absent on days 2 and 3 (Fig 1). This suggests that artesunate is a very potent antimalarial, it cleared all the parasites in the peripheral blood after only 2 days of treatment. However, it may not be potent enough to kill the sequestered parasites, hence the high recrudescent rate (Bunnag *et al,* 1990). This is supported by the *in vitro* finding that the action of artesunate is mainly at an early stage of asexual parasite development (Li *et al,* 1982; Jiang *et al,* 1982). We suggest that the therapeutic drug concentration should be maintained throughout the period of at least 3 cycles of schizogony in order to achieve a total eradication of asexual forms. With the use of pharmacokinetics of the drug as guidance, the proper dosage regimen will be

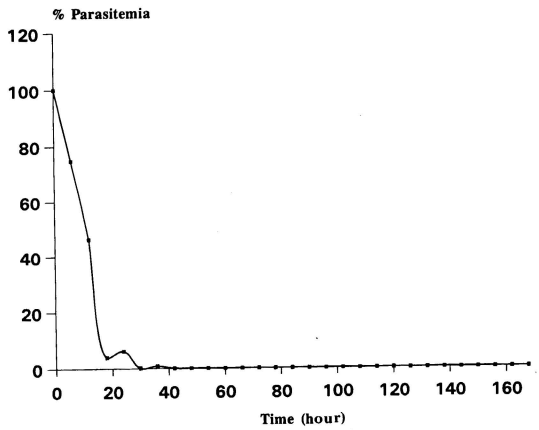

Fig 1—Parasitemia of patients in group A.

possible.

The appearance of *P. vivax* was found in 20-35% in this study is comparable to other studies (Bunnag *et al,* 1991; Pe Than Myint and Tin Shwe, 1986), confirming that artesunate is not effective against hypnozoite forms.

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