DOUBLE BLIND RANDOMISED CLINICAL TRIAL OF ORAL ARTESUNATE AT ONCE OR TWICE DAILY DOSE IN FALCIPARUM MALARIA

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Abstract. A double blind randomised comparative trial of the efficacy of daily dose (200 mg as an initial dose followed by 100 mg daily for another 4 days) and twice daily dose (100 mg 12 hourly for 2 doses on the first day, followed by 50 mg 12 hourly for another 8 doses) regimens of oral artesunate at 600 mg was studied in 59 Thai patients with uncomplicated falciparum malaria. Fifty patients had a complete 28-day follow-up period. Both regimens produced similar efficacy with no difference in adverse effects. The patients with the daily artesunate regimen had mean fever and parasite clearance times of 20 and 40 hours, respectively. The cure rate was 72%. Eight patients had recrudescence during days 15 to 28 while 8 showed *P. vivax* in their peripheral blood between days 12 and 21. The patients with the twice daily regimen had mean fever and parasite clearance time of 28 and 40 hours, respectively. The cure rate was 76%. Six patients had recrudescence during days 15 and 27 while 7 showed *P. vivax* during days 12 and 23.

We suggest that the duration of the treatment may be a more important factor determining the efficacy of artesunate rather than the frequency of the doses. Further studies based on pharmacokinetics are therefore needed to improve the cure rate to 100% to prevent the spread of *P. falciparum,* particularly in areas where there are high numbers of multi-drug resistant strains.

INTRODUCTION

Plasmodium falciparum in Thailand is highly resistant to chloroquine and sulfadoxine/pyrimethamine (Harinasuta *et al,* 1983) and there is increasing resistance to the alternative antimalarials qunine (Bunnag *et al,* 1987a) and even to mefloquine (Boudreau *et al,* 1982; Bunnag, unpublished observation). The combination of quinine and tetracycline is effective (more than 95% cure rate) in the hospital base but compliance seems to be a problem with home treatment due to side-effects, ie tinnitus. Alternative drugs are needed to combat drug-resistant strains and the poor compliance of the patients, ie such regimens must be effective with a short treatment course.

Artesunate (qinghaosu derivative) is another effective antimalarial drug with a rapid onset of action that destroys asexual parasites at an early stage of development (Li *et al,* 1982; Jiang *et al,* 1982). Artesunate rapidly cleared parasites with virtually no side-effects; however, with a one or three days course regimen of 600 mg (total dose) the recrudescent rate (RI) was 100%. Extending the treatment period to 5 days with a twice daily dose has been shown to improve the cure rate to 90% (Bunnag *et al,* 1990). A twice daily dose may not be an ideal regimen for the patients in the field, we therefore carried out a study to compare the efficacy of artesunate as a daily dose and as a twice daily dose with the same total dose in acute uncomplicated falciparum malaria.

MATERIALS AND METHODS

Patients

Fifty-nine falciparum malaria patients with acute uncomplicated malaria (asexual form parasitemia of less than 5%), aged between 15 and 52 years and weight range 43 to 63 kg, with no his-

tory of liver or kidney diseases 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.

Each patients 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 patients were admitted into the Bangkok Hospital for Tropical Diseases for 28 days.

Treatment

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

Group A : Artesunate 200 mg as an initial dose followed by 100 mg daily for another 4 days (test dose). The total dose was 600 mg.

Group B : Artesunate 100 mg 12 hourly for two doses on the first day, followed by 50 mg 12 hourly for another 8 doses (standard dose). The total dose was 600 mg.

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

Patients who failed to respond 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 count 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 gastrointestinal, central nervous, cardiovascular, dermatological, hematological systems and other changes possible attributable to artesunate.

Blood pressure (BP) 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 adverse-effects were compared between two therapeutic regimens. The parameters that used in determination included parasite clearance time (PCT), fever clearance time, the cure rate and the occurrence of adverse-effects.

RESULTS

Fifty-nine patients with acute uncomplicated falciparum malaria were recruited into the study. Only fifty patients had a complete 28-day follow-up period. The efficacy was then evaluated in these 50 patients, however, the FCT, PCT and the adverse effects were based on the data from 59 patients. Sixty-nine percent of the patients came from the eastern (Thai-Cambodian) border of Thailand, where highly 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 cases were found in either study group.

The patients with the daily artesunate regimen group had mean FCT and PCT of 20 and 40 hours, respectively. The 95% parasite clearance time was within 24 hours. Eight patients had recrudescence during days 15 to 28. The cure rate was 72%. Eight

Table 1

Clinical data on admission (presented as mean ± SD)

	Daily dose	Bid dose
Age (years)	24.6 ± 7.4	24.7 ± 9.7
Weight (kg)	52.1 ± 9.0	54.1 ± 7.5
Hematocrit (%)	35.7 ± 6.2	36.4 ± 7.4
WBC (/μl)	5,721 ± 1,931	5,987 ± 1,586
Temp (°C)	38.7 ± 0.7	38.8 ± 0.7
FBA (days)	5.1 ± 4.3	5.3 ± 7.3
Parasitemia (/μl)	12,129	16,443
(range)	(2,950 – 172,590)	(540 – 268,320)

patients showed *P. vivax* in their peripheral blood tients showed *P. vivax* in their peripheral blood between days 12 and 21 (Table 2).

The patients with the twice daily artesunate regimen had mean FCT and PCT of 28 and 40 hours, respectively. The 95% parasite clearance time was within 24 hours. Six patients had recrudescence during days 15-27. The cure rate was 76%. *P. vivax* infection was found in 7 patients during days 12-23 (Table 2).

There was no statistically significant difference between the two study regimens regarding PCT, FCT and 95% parasite clearance time. The occurrence of RI and the appearance of *P. vivax* during the 28-day follow-up were not significantly different.

Adverse effects

Artesunate was well tolerated with either regimen. Only one patient in group B (standard dose) had mild symptoms of dizziness on day 0-2 and itching without rash on days 2-6. The ECG, blood pressure and pulse rate showed no drug-associated changes in any of the patients. Erythrocyte counts, hematocrit levels, reticulocyte count, liver function tests and renal function were within normal limits throughout the study period.

***In vitro* sensitivity test**

Thirty-two isolates were sucessfully cultured and tested for minimum inhibitory concentration (MIC) of chloroquine, quinine, quinidine and mefloquine. Based on WHO criteria for *in vitro* sensitivity test, it was evident that all the isolates were resistant to chloroquine. The mean MIC for quinine, quinidine and mefloquine were shown to be high in comparison with a previous study (Thaithong *et al,* unpublished observations).

Table 2

Outcome of the treatment.

	Daily dose	Bid dose
PCT (hours)	39.7 ± 12.7	39.9 ± 11.6
FCT (hours)	20.4 ± 13.5	28.6 ± 23.8
P. vivax (cases)	8	7
S response	18 (72%)	19 (76%)
RI response	7 (28%)	6 (24%)

DISCUSSION

Artesunate at the total oral dose of 600 mg given over 5 days either in a daily dose or twice daily dose were well tolerated. The FCT and PCT were rapid. The initial response was excellent in all patients. Symptoms and parasites disappeared within 2 days after treatment. Short course treatment with virtually no adverse-effects makes artesunate a promising antimalarial for multidrug resistant falciparum malaria. The results of the present study confirmed the efficacy of artesunate

in a previous study (Bunnag *et al,* 1990). It is evident that the FCT and PCT were faster than those obtained from other antimalarials (Bunnag *et al,* 1987a; Harinasuta *et al,* 1983; Harinasuta *et al,* 1987). However, the rapid clearing of parasite followed by high recrudescent rates found in this study are in good agreement with the findings in the previous studies with artemether and qinghaosu (Pe Than Myint and Tin Shwe 1986; 1987; Li *et al,* 1982; 1984; China Cooperative Research Group on Qinghaosu and its Derivatives as Antimalarials, 1982).

It is unfortunate that very little is known about the pharmacokinetics of oral artesunate. It was claimed to have a very short half-life with intravenous administration (Li Guoquiao, unpublished observations). However, the daily oral dose and twice daily oral dose of artesunate in the present study resulted in a similar cure rate with no higher risk of adverse effects with either regimen. This suggests that artesunate may have a wide range of therapeutic index. The dosage regimen was not therefore based on pharmacokinetic properties of the drug, but rather on pharmacodynamic adjustment. The daily oral dose or twice daily doses did not seem to be an important factor affecting curative result. The duration of the treatment however, seems to play a significant role in successful treatment. It was shown in the previous study that the duration of 1 to 3 day treatment resulted in 100% recrudescent rate compared to 10% with 5 day treatment period (Bunnag *et al,* 1990). The results from the present study suggest that a duration of more than 5 days may be required in order to obtained 100% cure rate.

In area where multi-drug resistant strains of falciparum are well documented and rapidly increasing, the aim of the treatment should be 100% cure rate to prevent further spreading. The cure rate of 72-76% obtained from the present study is not considered as satisfactory for areas where high rates of drug resistant parasites exist. Further studies are therefore needed to assess the efficacy of artesunate tablets at the dose which would result in 100% cure rate in multi-drug resistant falciparum malaria.

Twenty-eight to 32 percent of patients in this study had vivax infections during days 12 to 23 after treatment. This could be explained by the findings in previous studies, which suggested that qinghaosu and its derivatives are effective against erythrocytic stages, but not exoerythrocytic stages of vivax infection (China Cooperative Research Group on Qinghaosu and its Derivatives as Antimalarials, 1982; Pe Than Myint and Tin Shwe, 1986). The appearance of vivax malaria is relatively early in comparison to those patients who were treated with mefloquine (Harinasuta *et al,* 1983) but comparable with the findings in quinidine treatment (Bunnag *et al,* 1987b). It may be due to the fact that mefloquine persisted in the blood longer than artesunate and quinidine. Either early or late reappearance of *P. vivax* suggests dynamically that these drugs have no action against hypnozoite forms.

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