PRELIMINARY REPORT: A COMPARATIVE CLINICAL TRIAL OF ARTEMETHER AND QUININE IN SEVERE FALCIPARUM MALARIA

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Abstract. Twenty-six patients with severe falciparum malaria were randomized to be treated with quinine or artemether. Twelve patients received quinine at the standard dose and fourteen patients received artemether intramuscularly at a total dose of 640 mg over 7 days. The patients were kept in the hospital for at least 7 days. Peripheral smear was performed 6-hourly until there was no parasitemia, then daily until discharged. Adverse effects were monitored through physical examination, laboratory findings and questionnaires. Laboratory examination was performed on admission, day 2, day 4 and weekly until discharged.

The patients in both groups were comparable in age, body weight, admission parasitemia, hemoglobin and white blood cell count. The survival rates were 93% and 58% in artemether and quinine groups, respectively ($p = 0.052$ at 95% confidence, using Fisher's exact test). The parasite and fever clearance times, and the time taken to gain consciousness in cerebral malaria patients were not significantly different between the two groups. Adverse effects in the quinine group consisted of dizziness and vertigo which were found in 4 patients. No adverse effects were noticed in the artemether group. This preliminary report suggests that artemether is a good alternative drug for severe falciparum malaria and seems to be better than quinine regarding survival rate and side effects. Confirmation of these findings in a larger study size is needed.

INTRODUCTION

Falciparum malaria constitutes one of the most serious public health problems in Thailand. Despite global efforts, malaria is still a highly prevalent disease in the tropics and is still a major cause of death. The mortality of severe malaria remains high, the treatment for complicated falciparum malaria (particularly that caused by multiple drug resistant parasites) remains unsatisfactory.

The ideal drug for severe malaria is that which stops vital parasite metabolic processes at all stages of development rapidly. Thus, the drugs that act earlier in the parasite cycle would be better for severe disease than those acting later in the cycle, as they would prevent maturation to the pathogenic phase (White and Krishna, 1989). Artemether has been shown to be a very potent antimalarial. It is active against severe falciparum malaria in China and Burma with a faster reduction of parasitemia than other antimalarial drugs (Li *et al,* 1982; China Cooperative Research Group on Qinghaosu and its Derivatives as Antimalarials, 1982; Wang and Xu, 1985; Pe Than Myint and Tin, 1986, 1987; Bunnag *et al,* 1990).

Quinine has been the drug of choice in severe falciparum malaria. However, the increase in quinine resistance in multiple drug resistant *P. falciparum* (Bunnag and Harinasuta, 1986) under scores the urgent need for alternative drugs.

We have investigated the efficacy of intramuscular artemether in severe malaria patients in comparison with the conventional treatment, *ie* quinine infusion.

MATERIALS AND METHODS

The study was carried out in the Prapokklao Hospital, Chantaburi. The study were done during May - December, 1991. Patients with severe falciparum malaria (WHO, 1990) with no history of antimalarials within 24 hours prior to admission,

aged between 15-45 years and weighed 45-60 kg, were recruited into the study. Written informed consent to participate in the study was obtained from all patients. The study was approved by the Ethics Committee of the Ministry of Public Health, Bangkok, Thailand.

The patients were admitted to the hospital for at least 7 days for completion of antimalarial therapy. The patients were requested to stay longer if they were unable to function independently or if parasites were still present in their peripheral blood.

Treatment

The patients were randomized to receive either quinine or artemether with following schedule:

Quinine group: A loading dose of quinine dihydrochloride at 20 mg/kg, followed by quinine dihydrochloride 10 mg/kg 8 hourly for 7 days, quinine sulfate tablets were given instead of quinine dihydrochloride as soon as the oral medication was possible.

Artemether group: Artemether 160 mg (Arthermin®) intramuscularly as loading dose, followed by 80 mg intramuscularly daily for another 6 doses.

Hemodialysis was performed in patients with renal failure, the decision was made by the attending physicians.

Clinical and laboratory investigations

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 discharged. Complete blood count and biochemistry were monitored on days 2, 4 and 7. ECG was performed in all patients on admission and patients with quinine once daily at 2 hours following infusion of the first dose of the day until parenteral quinine was discontinued. Patients with artemether had ECG recorded 6 hourly until 12 hours after the last dose. Chest x-ray was performed on admission. This was repeated serially when lung complications were detected.

Vital signs were recorded every 6 hours. Clinical status was evaluated on admission and twice daily for at least 7 days. Lumbar puncture was performed in all cerebral malaria patients on admission. Enrolment and antimalarial treatment began if the CSF was visually clear and subjects were removed from the study if subsequent microscopic examination suggested bacterial, viral or trauma etiology.

Patients with cerebral malaria were investigated for other causes of coma, including cerebrospinal fluid examination and culture, blood culture, hemagglutination-inhibition tests of acute-phase and convalescent-phase serum samples for dengue and Japanese B encephalitis. The blood culture was repeated at the time of death.

Data analysis

The therapeutic response (survival rate, FCT, PCT) and side effects were compared between the quinine and artemether groups. Survival rates were determined by the mortality at the end of the hospitalization period, *ie* 7 days. The rapidity of the response was based on fever and parasite clearance times (50% and 100% clearance times). The tolerance was based on both clinical and laboratory evaluations. FCT was the time for the temperature to fall below 37.5°C and remain that value for 72 hours. PCT was the time for the parasite count to fall below the level of microscopic detection (thick film).

Statistical analysis

Comparison of normal distributed data was by Student's *t* test. The Mann Whitney U-test was applied if data were not normally distributed. Parasite counts were compared after logarithmic transformation and clearance times were calculated from normalized values. Proportional data were compared by Fisher's exact test (survival rate, side effects).

RESULTS

Twenty-six patients were included in the study (25 males and one female); 16 patients presented with cerebral malaria (7 in the quinine and 9 in the artemether groups). Twelve patients received quinine and 14 had artemether. The patients in both groups were comparable in age, body weight, admission parasitemia, hemoglobin and white

Table 1

Clinical presentation.

	Quinine N = 12	Artemether N = 14
Mean (SD)		
Age (years)	31.7 (10.4)	30.4 (10.0)
Weight (kg)	54.4 (7.7)	52.8 (6.8)
Hct (%)	32.9 (7.5)	32.0 (7.3)
Mean (range)		
Parasitemia (per μl)	117,489 (16,200-520,520)	89,125 (15,550-429,120)
No. of cases		
Jaundice	4	7
Renal failure	3	7
Cerebral malaria	7	9
Hyperparasitemia	2	2

Table 2

Therapeutic response.

	Quinine N = 12	Artemether N = 14
Mean (SD)		
FCT (hours)	94.0 (34.7)	64.3 (27.8)
PCT (hours)	61.6 (12.6)	63.3 (30.0)
50% PCT (hours)	13	7.5
Survival rate (%)	58	93
Cause of death (N)		
Cerebral malaria	3	0
ARDS	2	0
Shock	0	1

blood cell count (Table 1). The severity of the disease was not different between groups (Table 1).

The FCT and PCT between the two groups were not statistically different: 94.0 and 64.3 hours, 61.6 and 63.3 hours for quinine and artemether groups, respectively (Table 2). The parasite clearance curves of the two groups are shown in Fig 1. The 50% parasite clearance times were 13 and 7.5 hours for quinine and artemether groups, respectively. No patients showed RII or RIII type of response in either treatment group. The times to gain consciousness in cerebral malaria patients were 52 and 47 hours in quinine and artemether groups, respectively. Three cerebral malaria patients in the quinine group died, while all survived in the artemether group. No cerebral malaria patients who survived in either group had any sequelae after recovery.

Overall 6 patients died, 5 in the quinine group and 1 in the artemether group. The survival rates were 58% and 93% in the quinine and artemether groups, respectively ($p = 0.052$, at 95% confidence). The causes of death of these patients are presented in Table 2.

Acute renal failure was found in 10 patients, 3 in the quinine group and 7 in the artemether group. All three renal failure patients in the quinine group required hemodialysis. In spite of early

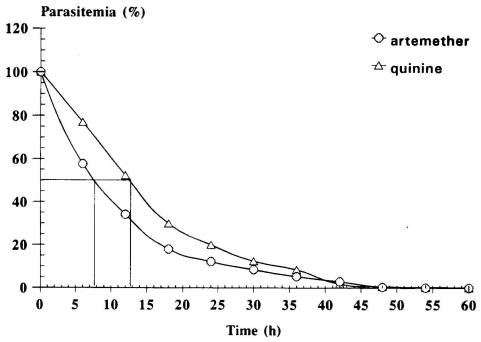

Fig 1—Parasite clearance curve.

hemodialysis, two patients died. All renal failure patients in the artemether group survived, only 3 of them required hemodialysis.

There were no significant drug-related changes in laboratory findings or ECG with either drug. The side effects in the quinine group were dizziness and vertigo. No side effects were detected with artemether.

DISCUSSION

Artemether is an effective alternative antimalarial to quinine in the treatment of severe falciparum malaria. The dose used in this study was slightly higher than the regimen recommended in China (600 mg given over 5 days). Artemether was well tolerated in severe malaria patients. There were no detectable systemic side effects or evidence of any untoward hematological or biochemical effects within the 7 day observation period in this limited number of patients.

The clinical parameters observed from the present study were similar in the two treatment groups. The speed of parasite clearance was not different between artemether and quinine (Fig 1). This is in contrast with the findings in uncomplicated malaria where artemether was associated with more rapid reduction in parasitemia than any other available antimalarials (China Cooperative Research group on Qinghaosu and its Derivatives as Antimalarials 1982; Li *et al,* 1982; Bunnag *et al,* 1990). These findings are in agreement with a recent study in Gambian children where the speed of parasite clearance was faster with artemether than chloroquine in moderately severe malaria but the rate of parasite clearance was not different in severe malaria (White *et al,* 1992). Although the PCT and FCT and time taken to regain consciousness in the artemether and quinine groups were similar, the survivor rate tended to be higher in the artemether group (93% and 58% for artemether and quinine groups, respectively; $p = 0.052$). It should be noted that all patients with cerebral malaria in the artemether group survived while the survival rate for cerebral malaria in the quinine group was only 57% (4/7). This suggests that artemether stops the development of the parasites rapidly, limiting further sequestration and damage. In contrast to quinine, the action may be slower; and further sequestration and damage may have taken place. Further studies with a larger group size are needed to show significant differences in survival rate to support this hypothesis.

All those patients who presented with acute renal failure in the artemether group survived, in contrast to those in the quinine group where 2 out of 3 died in spite of early hemodialysis. Although the difference is not statistically significant ($p = 0.06$), it suggests that artemether may be better than quinine in malaria patients with acute renal failure. A larger study size would be necessary to confirm this finding.

We conclude that artemether is promising in severe falciparum malaria and can be considered as an alternative therapy to quinine. Quinine has been the drug of choice for severe falciparum malaria in Thailand but its association with a prolongation in parasite and fever clearance times and an increase of RII type of response (Karbwang and Harinasuta, 1992) will soon limit the use of quinine in severe falciparum malaria in this country. Artemether is well tolerated and easier to administer than quinine. Although the speed of parasite clearance did not differ from that with quinine, the survival rate tended to be higher. The apparent greater efficacy of artemether in acute renal failure patients also needs to be highlighted, but again requires confirmation by a larger study.

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REFERENCES

Bunnag D, Harinasuta T. The current status of drug resistance in malaria. In: Howell M, ed. Parasitology Quo Vadit? Australian Academy of Science 1986; pp 180-96.

Bunnag D, Viravan C, Looareesuwan S, Karbwang J, Harinasuta T. High efficacy of artemether on multidrug resistant falciparum malaria. Presented at the VII International Congress of Parasitology, Paris, August 20-24, 1990.

China Cooperative Research Group on Qinghaosu and its Derivatives as Antimalarials. Clinical studies on the treatment of malaria with qinghaosu and its derivatives. *J Tradit Chin Med* 1982; 2 : 45-50.

Karbwang J, Harinasuta T. Distribution of drug resistance. In: Karbwang J, Harinasuta T, eds. Chemotherapy of Malaria in Southeast Asia. Bangkok: Ruamtasana 1992; 48-72.

Li G, Guo X, Jin R, Wang Z, Jian H, Li Z. Clinical studies on treatment of cerebral malaria with qinghaosu and its derivatives. *J Tradit Chin Med* 1982; 2 : 125-30.

Pe Than Myint, Tin Shwe. The efficacy of artemether (Qinghaosu) in *Plasmodium falciparum* and *P. vivax* in Burma. *Southeast Asian J Trop Med Public Health* 1982; 17 : 19-22.

Pe Than Myint, Tin Shwe. A controlled clinical trial of artemether (qinghaosu derivative) versus quinine in complicated and severe falciparum malaria. *Trans R Soc Trop Med Hyg* 1987; 81 : 559-61.

Wang T, Xu R. Clinical studies of treatment of falciparum malaria with artemether, a derivative of qinghaosu. *J Tradit Chin Med* 1985; 5 : 240-2.

White NJ, Krisana S. Treatment of malaria: some considerations and limitations of the current methods of assessment. *Trans R Soc Trop Med Hyg* 1989; 83 : 767-77.

White NJ, Waller D, Crawley J, *et al.* Comparison of artemether and chloroquine for severe malaria in Gambian children. *Lancet* 1992; 339 : 317-21.

World Health Organization, Severe and complicated malaria. *Trans R Soc Trop Med Hyg* 1990; 84 (suppl 2) : 1-65.