

# ARTEMETHER 5 VERSUS 7 DAY REGIMEN FOR SEVERE FALCIPARUM MALARIA

Juntra Karbwang, Kesara Na-Bangchang, Yupaporn Wattanakoon, Aurathai Thanavibul and Tranakchit Harinasuta

Clinical Pharmacology Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

**Abstract.** Twenty-eight male Thai patients with severe falciparum malaria were randomized to receive either artemether for a 5 (300 mg initial dose followed by 100 mg for another 4 days) or a 7 days regimen (160 mg initial dose, followed by 80 mg daily for another 6 days). Thirteen patients received a 5 day regimen and 15 received 7 day regimen. The follow-up period was 28 days. The patients in both groups were comparable in age, body weight, admission parasitemia, hematocrit and white cell count. There were 4 patients in each group who presented with cerebral malaria.

The median values of parasite and fever clearance times (PCT and FCT) in the 5 and 7 days regimens were 52 vs 60 hours, and 85 vs 68 hours, respectively. There were 8 and 4 patients, respectively who had recrudescence during days 15 to 25. The cure rates were 38% (95% CI = 14-68%) and 73% (95% CI = 50-96%), respectively for 5 and 7 day regimens. None died in either group. No patients in either group had neurological sequelae after recovery of consciousness.

Clinically adverse effects in either group were transient pain at the site of injection. No drug related biochemical or ECG changes were noted in either group. The duration of treatment is the determinant of the cure rate; however, the duration of even 7 days still resulted in high recrudescence rate. It may be necessary to combine artemether with other longer half-life antimalarials to improve the cure rate.

## INTRODUCTION

Falciparum malaria is still one of the most prevalent infectious diseases of the tropics and one of the major causes of death in the world due to the disease itself and its complications. The use of artemether in acute uncomplicated and moderately severe falciparum malaria has been shown to be effective against multidrug resistant falciparum malaria (Bunnag *et al*, 1991; 1992). The 95% parasite clearance time was within 24 hours and fever was subsided within 48 hours. The initial responses were excellent in both uncomplicated and severe malaria. However, a high recrudescence rate, particularly in moderately severe malaria had been noticed (Bunnag *et al*, 1992). This seems to be an unsolved problem. Different dosage regimens have been studied but there has not yet been any strong evidence to support any particular regimen as the most effective. There is still anarchy with regard to dose levels and regimens which have been inconsistently chosen and not subject to serious comparison.

The efficacy of artemether has been shown to be superior to quinine in severe falciparum malaria, based on the mortality and time to regain conscious-

ness (Karbwan *et al*, 1994; Taylor *et al*, 1993; Win *et al*, 1992). However, none of these studies has provided the cure rate from the regimen used. It is likely that the use of this drug to treat severe malaria will be extensive in areas with multidrug resistant falciparum malaria, and therefore it is important to focus further studies on determining optimum therapeutic dosage regimens.

We have carried out a study to evaluate the cure rates of two regimens of artemether in the treatment of severe falciparum malaria.

## MATERIALS AND METHODS

### Patients

The study was carried out in the Bangkok Hospital for Tropical Diseases, Bangkok, Thailand, an area where there is no malaria transmission, thus reinfection can be excluded. Male patients with severe falciparum malaria (Warrell *et al*, 1990), with no history of antimalarial treatment, aged between 15-65 years and weighing 45-75 kg, were recruited into the study. The patients were admitted to the

hospital for 28 days. Patients with concurrent diseases were not included. Written informed consent for participation in the study was obtained from all patients. The study was approved by the Ethics Committee of the Ministry of Public Health, Bangkok, Thailand.

### Treatment

Patients were randomized to receive artemether at either 5 or 7 day regimen as follows:

(1) *5 day regimen*: A loading dose of 300 mg intramuscular artemether, followed by 100 mg daily for 4 days; (2) *7 day regimen*: A loading dose of 160 mg intramuscular artemether, followed by 80 mg daily for another 6 days

In either group, artemether tablets were given instead of intramuscular artemether as soon as the oral medication was possible. Dialysis was performed in patients with acute renal failure (ARF); 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, and baseline antimalarial levels (mefloquine and quinine). Parasite count was performed every 6 hours until negative (thick and thin film) then daily until day 28. Complete blood count and serum biochemistry were monitored on days 2, 4, 7, 14, 21 and 28. ECG was performed on admission in all patients, then 6 hourly until 12 hours after the last dose. Chest x-ray was performed on admission. This would be repeated serially if 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 to exclude other causes of coma. Enrolment and antimalarial treatment began if the CSF was visually clear; patients were removed from the study if subsequent microscopic examination suggested bacterial, viral infections or trauma etiology.

### Data analysis

The therapeutic response (SR: survival rate; FCT and PCT: fever and parasite clearance times; the cure

rate) and adverse effects were compared between the two groups. SR was determined by the mortality at the end of the hospitalization period. The repidity of the response was based on FCT and PCT (100% clearance time). The tolerance was based on both clinical and laboratory evaluations. The cure rate was evaluated in patients who completed the 28 day follow-up period. PCT was the time taken for the parasite count to fall below the level of microscopic detection (thick film). FCT was the time taken for the temperature to fall below 37.3°C and remain at that value for a least 24 hours.

### Statistical analysis

Comparison of normal distributed data between the 2 groups was by student's *t* test. Mann Whitney U-test was applied if data were not normally distributed. Parasite count was compared after logarithmic transformation and clearance from normalized values. Proportional data were compared by chi-square test (*ie* cure rate).

## RESULTS

Twenty-eight male Thai patients with severe falciparum malaria were recruited into the study; 13 patients received a 5 day regimen and 15 received a 7 day regimen.

There were 4 cerebral malaria patients in each group, the rest of the patients were presented with other severe manifestations of malaria (*ie* renal failure, jaundice, hypertension, and anemia). There were 3 patients who had renal failure on admission (1 and 2 in the 5 and 7 day regimens, respectively); all required hemodialysis.

The patients in both groups were comparable in age, body weight, admission parasitemia, hematocrit, white cell count (Table 1). No patients had previous treatment based on the baseline drug concentration.

All patients had a good initial response, the median values of PCT and FCT in the 5 and 7 day regimens were 52 vs 60 hours, and 85 vs 68 hours, respectively. The PCT and FCT were not statistically significantly different between the 2 groups (Table 2). There were 12 patients who had recrudescence between days 15 to 25 (8 in the 5 day regimen and 4 in the 7 day regimen). The cure rates were 38% (95% CI = 14-68%) and 73% (95% CI = 50-96%), respectively for

Table 1  
Admission clinical data.

	Artemether 5 days	Artemether 7 days
<b>Median (range)</b>		
Age (yr)	25.5 (15-37)	22.0 (15-39)
Weight (kg)	51.0 (40-65)	51.0 (45-63)
Hct (%)	38.5 (20-49)	38.0 (16-49)
WBC ( $\times 10^3/\mu\text{l}$ )	7.2 (4.2-17.2)	6.6 (2.9-9.2)
Admission parasitemia ( $/\mu\text{l}$ )	354,415 (132,600-678,240)	388,800 (4,890-1,402,200)
No. of patients with coma	4	4

Table 2  
Outcome of the treatment.

	Artemether 5 days (N = 13)	Artemether 7 days (N = 15)
Included in data	13	15
Survival rate (%)	100	100
Cure rate (%)	38	73
FCT (hours)	84.5 (34-215)	68.0 (9-228)
PCT (hours)	52.0 (30-105)	60.0 (37-141)

5 and 7 day regimens. These cure rates, however, were not statistically different ( $p = 0.0629$ , 95% CI = 0.002-0.695). None of the cerebral malaria patients had neurological sequelae after treatment.

Mild and transient pain at the injection site occurred for approximately 15 minutes after artemether injection, but no abscess was noticed in any patient. No other clinical side-effects were observed. There were no significant changes in ECG which would suggest any effect of artemether on the cardiac system. Bradycardia was not found in any of the patients. No drug-associated changes in hematological or biochemical test was noted in either group.

## DISCUSSION

The present study confirms the efficacy of artemether against severe falciparum malaria in previous reports (Bunnag *et al*, 1992; Karbwang *et al*, 1994; Myint and Shwe 1987; Myint *et al*, 1989; Shwe

*et al*, 1988; 1989; Win *et al*, 1993). However, the recrudescence rate was rather high, particularly in the 5 day regimen. This is the first comparative study of the 2 regimens with different duration of artemether in severe malaria. The results suggested that the duration of treatment has a significant role in the evaluation of cure rate, but not the initial response. The action of artemether has been suggested to be confined to the small ring stage (Jiang *et al*, 1982; Qinghaosu Antimalarial Coordinating Research Group, 1979), it rapidly clears the parasites in the circulation, but not the sequestered parasites. In severe malaria, a number of sequestered trophozoites and schizonts in different tissue capillaries are expected. The development of these parasites may be suppressed but the parasites still survive during treatment period. Eventually, under optimum conditions, the young rings are released to the circulation at the time when artemether is no longer present due to its short half-life (China Cooperative Research Group, 1982; Na-Bangchang *et al*, 1994; Zhou *et al*, 1988). Recrudescence has been

observed as early as 7 days after administration of a single dose of artesunate (Bunnag *et al*, 1991), suggesting that it requires at least 4-5 parasite cycles after drug administration for sequestered parasites to be seen in the peripheral blood. It has thus been suggested then that treatment or the drug concentrations should be sufficient to cover this period.

In this study, the earliest reappearance of parasites was on day 15 and the latest was 25 days. Unlike mefloquine, where the reappearance of the parasites could occur even 28 days after drug administration (Karbawang *et al*, 1992), the recrudescence with artemisinin compounds can be expected to occur within 28 days (Bunnag *et al*, 1992; Karbwang *et al*, 1992). This suggests that a follow-up of 28 days is sufficient for evaluating the cure rate from artemether.

In uncomplicated falciparum malaria, the cure rate of 5 day regimen of artemether was 92% (Bunnag *et al*, 1992). This high cure rate could possibly be explained by the presence of mostly ring form parasites in the peripheral blood exceeding those sequestered in the tissues. The cure rate in the present study was significantly lower than in the previous study with the same duration of treatment *ie*, 5 days (92 vs 38%,  $p = 0.001$ , Bunnag *et al*, 1992). When the duration of treatment was extended to 7 days, there was a trend of increasing in cure rate (from 38% to 73%), though this difference was not statistically significant ( $p = 0.0629$ ). However, this cure rate is still considered as inadequate.

There seems to be a consistent association between using artemether alone and high recrudescence rate (Myint *et al*, 1989; Bunnag *et al*, 1992), even with 7 day treatment duration in the present study. Extending the treatment to more than 7 days may increase the cure rate, but patients' compliance is likely to be poor. The results of the present study suggest that it is unlikely to use artemether successfully (*ie* high cure rate) as a single drug in the treatment of severe falciparum malaria. Using artemether in combination with mefloquine has been shown to reduce the recrudescence rate in severe falciparum malaria (Shwe *et al*, 1988; 1989). The alternative use of artemether in severe malaria should be therefore, to combine it with other effective long half-life antimalarials (*eg* mefloquine) rather than using it alone, to ensure a better cure rate. Determination of optimum dosage regimen of the combination requires further studies.

## ACKNOWLEDGEMENTS

We are grateful to the assistance of the staff of Hemodialysis Unit, Ward 7 and ICU, Hospital for Tropical Diseases, Bangkok. We thank Ms Kunya Ucachok for her assistance on data analysis and Professor Tan Chongsuphajsiddhi for his continuing support.

## REFERENCES

- Bunnag D, Viravan C, Looareesuwan S, Karbwang J, Harinasuta T. Clinical trial of artesunate and artemether on multidrug resistant falciparum malaria in Thailand: A preliminary report. *Southeast Asian J Trop Med Public Health* 1991; 22:380-5.
- Bunnag D, Karbwang J, Harinasuta T. Artemether in the treatment of multidrug resistant falciparum malaria. *Southeast Asian J Trop Med Public Health* 1992; 23: 762-7.
- China Cooperative Research Group on Qinghaosu and Its Derivatives as Antimalarials. Clinical studies on the treatment of malaria with qinghaosu and its derivatives. *J Trad Chin Med* 1982; 2: 45-50.
- Jiang JB, Li GQ, Guo XB, Kong YC, Arnold K. Antimalarial activity of mefloquine and qinghaosu. *Lancet* 1982; 2: 285-8.
- Karbawang J, Na-Bangchang K, Thanavibul A, Bunnag D, Chongsuphajsiddhi T, Harinasuta T. Comparison of oral artemether and mefloquine in acute uncomplicated falciparum malaria. *Lancet* 1992; 1: 1245-8.
- Karbawang J, Tin T, Sukontason K, *et al*. Effect of artemether on mortality of severe falciparum malaria. 1994 (submitted).
- Myint PT, Shwe T. 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.
- Myint PT, Shwe T, Soe L, Htut W. Clinical study of the treatment of cerebral malaria with artemether (qinghaosu derivative). *Trans R Soc Trop Med Hyg* 1989; 83: 72.
- Na-Bangchang K, Karbwang J, Thomas CG, *et al*. Pharmacokinetics of artemether after oral administration to healthy Thai males and patients with acute uncomplicated falciparum malaria. *Br J Clin Pharmacol* 1994; 37: 249-53.
- Qinghaosu Antimalarial Cooperative Research Group. Antimalarial studies on qinghaosu. *Chin Med J* 1979; 92:811-6

- Shwe T, Myint PT, Htut Y, Myint W, Soe L. The effect of mefloquine-artemether compared with quinine on patients with complicated falciparum malaria. *Trans R Soc Trop Med Hyg* 1988; 82: 665-7.
- Shwe T, Myint PT, Htut Y, Myint W, Soe L, Thwe M. Clinical studies on treatment of cerebral malaria with artemether and mefloquine. *Trans R Soc Trop Med Hyg* 1989; 83: 489.
- Taylor TE, Wills BA, Kazembe P, *et al.* Rapid coma resolution with artemether in Malawian children with cerebral malaria. *Lancet* 1993; 1: 661-2.
- Warrell DA, Molyneux ME, Beales PF. Severe and complicated malaria. *Trans R Soc Trop Med Hyg* 1990; 84 (suppl): 1-65..
- Win K, Than M, Thwe Y. Comparison of combinations of parenteral artemisinin derivatives plus oral mefloquine with intravenous quinine plus oral tetracycline for treating cerebral malaria. *Bull WHO* 1992; 70: 777-82.
- Zhou ZM, Huang YX, Xie GH, *et al.* HPLC with polarographic detection of artemisinin and its derivatives and application of the method to the pharmacokinetic study of artemether. *J Liq Chromatogr* 1988; 11: 1117-37.