ARTEMETHER IN MODERATE TO SEVERE MALARIA: A MULTICENTER TRIAL IN INDIA

PC Bhattacharya[1], AJ Pai-dhungat[2], and K Patel[3]

[1]Department of Medicine, Guwahati Medical College, Guwahati, India; [2]Department of Medicine, BYL Nair Hospital, Bombay, India; [3]Department of Medicine, Medical College/SSG Hospital, Vadodara, India

Abstract. 154 patients suffering from acute attack of moderate to severe malaria caused by *Plasmodium falciparum* were treated with 480 mg artemether, administered intramuscularly (IM) in six equally divided doses at 12 hour intervals. Results showed a rapid parasite clearance. Mean parasite clearance time (PCT) was found to be 23.65 ± 1.57 hours. Mean fever clearance time (FCT) was 35.28 ± 1.7 hours. Adverse drug events (ADE) were mild and self-limiting. Recrudescence rate (RR) among the patients followed up was 4.55%. We conclude that artemether is a safe and effective anti-malarial agent for the treatment of moderate and severe cases of *P. falciparum* malaria.

INTRODUCTION

Due to the sheer number of clinical cases occurring every year, malaria is one of the most important vector-borne diseases. Since the late seventies, there has been a global rise in the incidence of malaria every year. Global ecological changes have contributed significantly to this resurgence. It is anticipated that if ecological changes continue in the same manner resulting in global warming, the incidence of vector borne diseases would rise even further (Sharp, 1996).

More serious than the increase in number is the problem of development of resistance of malarial parasites, particularly *P. falciparum*, to conventional anti-malarials. *P. falciparum* resistance, first reported in Thailand in 1957, spread across Southeast Asia and resistant strains have now appeared in most of the malarious world including India (Hoffman, 1996). Parenteral quinine reemerged as the principal agent for severe drug resistant malaria. However, RII type resistance to quinine has been recently reported from Southeast Asia (Karbwang *et al*, 1995). Alternative drugs for the treatment of drug resistant malaria are therefore urgently needed.

Among the alternatives to quinine, the artemisinin derivatives have attracted special interest because of the rapidity with which they reduce *P. falciparum* parasitemia (van Hensbrocke *et al*, 1985). Locally known as Qinghaosu, artemisinin has been in use in China for many centuries but scientific rediscovery of its active principle was made in 1972, and since 1978, artemisinin and its derivatives have been officially registered for treating malaria patients in China (Klayman, 1985).

Artemisinin is obtained from a medicinal plant, *Artemisia annua*. It is an anti-malarial agent with a chemical structure unlike any other (non nitrogenous heterocycle). The compound is a sesquiterpene lactone characterized by an endoperoxide linkage which is extremely unusual in an antimalarial compound. Structure-activity studies have shown that the presence of this peroxide bridge is essential for antimalarial activity (Luo and Shen, 1987; WHO, 1986). Artemisinin is, however poorly soluble in water and therefore, difficult to handle therapeutically. Chemical modifications of artemisinin have enabled more powerful derivatives to be obtained.

Artemether is a methylether derivative of artemisinin and is developed for intramuscular injection by dissolving it in groundnut oil. It is a schizonticidal agent acting at the asexual erythrocytic phase of the parasite (Klayman, 1985) and is much more active than the parent compound (Hien and White, 1993). Various studies carried out all over the world have proved its safety and efficacy in malaria.

We report the first multicentric clinical trial with artemether in Indian patients which was conducted with the main objectives to test its safety, efficacy and tolerance in the Indian population.

The study was designed as single blind, non-comparative, multicentric trial, carried out during the period between January to December 1994. Prior permission was obtained from Institutional Ethics Committee. The protocol was also approved by the Indian Council of Medical Research. Informed written consent was obtained from patients before administering the drug. The study was conducted at BYL Nair Hospital, Bombay, Guwahati Medical College, Guwahati, and Medical College/SSG Hospital, Vadodara, using a common protocol.

MATERIALS AND METHODS

Patients

Adult hospitalized patients of either sex, presenting with symptoms of acute moderate to severe malaria, having a positive peripheral smear (PS) for asexual forms of *P. falciparum*, with a parasite count of 3,000 or more per mm^3 and history of not having taken any treatment for the present illness or having been treated without positive response (resistant cases), were included in the study. Patients having signs of severe malaria as defined by WHO were also included with the exception of severe anemia (Hb < 5 gm%). Pregnant or lactating females, patients having a hemoglobin less than 5 g%, concomitant progressive fatal disease, significant renal impairment or evidence of hepatic/cardiac failure were excluded from the study.

Treatment

1 ampoule of artemether [Paluther: Rhone Poulenc (India) Ltd] containing 80 mg/ml to be injected intramuscularly twice a day for 3 days.

Clinical and laboratory investigations

On inclusion in the study, patients were subjected to baseline investigations on day 1 which were then repeated on day 7. Whenever possible the tests were repeated on days 14, 21 and 28 of the study. These investigations included complete blood count, reticulocyte count, SGPT, SGOT, alkaline phosphatase, serum creatinine, blood urea and serum albumin. Temperature, respiratory rate and pulse rate were recorded every 6 hours for the first 48 hours and then every 8 hours. Blood pressure was recorded every 12 hours during hospitalization.

Malarial parasite count was done at the time of admission by preparing a thin and a thick smear from finger prick blood, stained by Giemsa stain before starting the treatment and repeated every six hours until four consecutive parasite smear examinations were negative. Subsequently it was repeated on days 7, 14, 21 and 28 of therapy or SOS in between if patient reported back with fever. Parasite count was done by counting the number of asexual forms of parasites /200 WBC in thick smear and multiplying it by the total WBC count at the time.

Data analysis

Efficacy of the drug was evaluated by clinical assessment of patient and by finding out the parasite clearance time (PCT) and fever clearance time (FCT). FCT was defined as the time from the start of treatment until the oral temperature fell to 37.5°C or below and did not rise again. PCT was calculated as time taken from the start of the treatment until the first time the negative smear was obtained and persisted so for 24 hours. Negative smear is defined as complete absence of parasites in thick film after screening at least 20 fields.

Overall clinical assessment of patients was given on the basis of daily recording of signs and symptoms and PCT and FCT. Safety evaluation was done by laboratory parameters mentioned earlier. Concomitant treatment was kept to minimum in the form of antipyretics given SOS if temperature was more than 102°F.

Adverse drug events (ADEs), whether volunteered by patient or observed by treating physician were carefully noted.

Statistical analysis

Results were analysed statistically by using Chi square test and Wilcoxon rank sumtest. Analysis was carried out at 5% level of significance.

RESULTS

A total of 154 patients were enroled in the study. The patient enrolment data is shown in Table 1. Tables 2 and 3 show demographic features and clinical profile, respectively. Table 4 shows the pattern of clinical response of patients to artemether. The mean time taken for all symptoms except hepato- and splenomegaly to disappear was 2.82 days.

Table 1

Patient enrolment data.

No. patients enroled	154
No. drop-outs	0
No. Patients analyzed Day 7	154
No. patients followed up	
Day 14	142
Day 21	125
Day 28	107

Mean FCT was 35.28 ± 1.70 hours. There was a statistically significant fall in the body temperature at the end of 6 hours as compared to baseline values ($p < 0.05$). The p-values continuously showed significance after 6 hours. Mean PCT was 23.65 ± 1.57 hours. There was significant fall in parasite count at 6 hours as compared to baseline and continued to remain significant thereafter for both ($p < 0.0001$). The patterns of fall in body temperature and parasite counts are shown in Figs 1 and 2, respectively.

Artemether was well tolerated by most patients. ADE was observed in 7 out of 154 patients (4.5%) of which one case was definitely related to medication, that of pain at the injection site. In the rest of the cases the case-effect relationship of the adverse event with the drug could not be conclusively proved. The hematological and biochemical parameters remained within normal laboratory range after the treatment.

Of 154 patients enroled in the study, recrudescence was observed in 7(4.55%) patients. The details are given in Table 5.

DISCUSSION

The present study confirms the safety and efficacy of artemether in malaria and is comparable to those reported previously of the use of artemether in the treatment of acute uncomplicated and moderately severe falciparum malaria (Bunnag *et al*, 1992). As in the case of other studies with artemether, this study also clearly shows that the parasite is cleared very rapidly from the blood. Artemether is known to act on the ring stage thus preferentially accelerating the clearance of young parasites and halt the process of sequestration of parasites in the red blood cells thus stopping further tissue destruction.

The safety of artemether has also been established in this study. The only adverse event related to the drug was pain at th site of injection seen in one patient. Artemether may be a practical alternative to quinine in the treatment of severe malaria since several studies have shown artemether to be as effective or better than quinine with particular reference to coma resolution time and parasite clearance time. These studies also report that artemether has a better adverse event profile including less irritation at the site of injection (van Hensbroke *et al*, 1996; Myint and Shwe, 1987) and at a once a day dose.

Unlike mefloquine where the reappearance of

Table 2

Demographic data.

Total patients	Sex		Age	Body weight	Patients with chloroquine recrudescence
	Male	Female	(mean years)	(mean kg)	
154	114	40	30.95 ± 1.08	50.11 ± 1.01	12 (7.79%)

Table 3
Clinical profile on admission.

Symptomatology	No. patients (%)
Fever	154 (100)
Paroxysm with rigors and flush	151 (98.05)
Headache	130 (84.42)
Nausea	90 (58.44)
Vomiting	75 (48.70)
Diarrhea	19 (12.34)
Myalgia	81 (52.70)
Jaundice	16 (10.39)
Edema	1 (0.65)
Debilitation	10 (6.49)
Prostration	21 (13.64)
Cough	35 (22.73)
Pulmonary edema	1 (0.65)
Oliguria	5 (3.25)
Circulatory collapse	2 (1.30)
Mental confusion	12 (7.79)
Coma	1 (0.65)
Encephalopathy	3 (1.95)
Liver tenderness	42 (27.27)
Spleen tenderness	47 (30.52)
Hepatomegaly	76 (49.35)
Splenomegaly	113 (73.38)

Table 4
No. days in which symptoms disappeared.

Symptoms	Days (mean)
Rigors and flush	2.59
Headache	2.85
Nausea	2.52
Vomiting	2.23
Diarrhea	2.58
Myalgia	2.89
Jaundice	5.95
Edema	2.00
Debilitation	3.60
Prostration	2.81
Cough	3.57
Circulatory collapse	2.00
Pulmonary edema	2.00
Oliguria	2.00
Coma	2.00
Mental confusion	2.67
Encephalopathy	2.67
Liver tenderness	3.55
Spleen tenderness	3.21
Fever and hepato/splenomegaly analysed separately	

Table 5
Recrudescence rate.
No (%) patients = 7 (4.5%)

Day of follow-upon which recrudescence	No. of patients
9	1
14	2
17	1
21	2
24	1

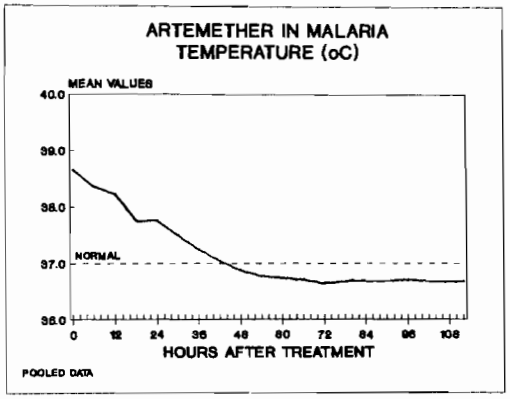

Fig 1–Artemether in malaria temperature (0°C).

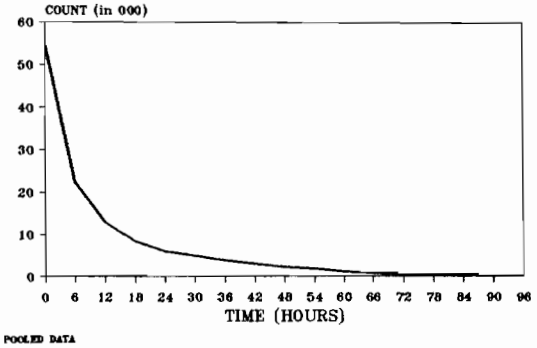

Fig 2–*P. falciparum* count. (Interpolated data) Mean clearance time = 24.04 + 1.6

the parasites could occur even 28 days after drug administration, the recrudescence with artemisinin compounds can be expected to occur within 28 days (Karbwang *et al*, 1994). Thus a follow up of 28 days is sufficient for evaluating the cure rate from artemether. It is noteworthy that of the seven patients who reported with recrudescence, five

(3.02%) had recrudescence between 14 and 21 days, a period more likely to show true recrudescence.

Artemether thus appears to be an important addition to the antimalarials for the treatment of severe malaria particularly in the light of reports of quinine resistance.

ACKNOWLEDGEMENTS

The authors would like to thank the Medical Department of Rhone Poulenc (India) Ltd for their help in designing the protocol and supplying the samples.

REFERENCES

Bunnag D, Karwang J, Harinasuta T. Artemether in the treatment of multidrug resistant falciparum malaria. *Southeast Asian J Trop Med Public Health* 1992; 23 : 762-7.

Hien TT White NJ. Qinghaosu. *Lancet* 1993; 341 : 603-8.

Hoffman SL. Artemether in severe malaria. *N Engl J Med* 1996; 335 : 124-5.

Karbwang J, Na Bangchang K, Watanakul Y, Tanavibul A, Harinasuta T. Artemether 5 versus 7 day regimen for severe falciparum malaria. *Southeast Asian J Trop Med Public Health* 1994; 25 : 702-6.

Karbwang J, Tin T, Rimchala W, *et al.* Comparison of artemether and quinine in the treatment of severe falciparum malaria in south-east Thailand. *Trans R Soc Trop Med Hyg*, 1995; 89 : 668-71.

Klayman DL Qinghaosu (artemisinin) : an antimalarial drug from China. *Science* 1985; 228 : 1049-55.

Luo XD, Shen CC. The chemistry, pharmacology and clinical applications of qinghaosu (artemisinin) and its derivatives. *Med Res Rev*, 1987; 7 : 29-52.

Myint PT, Shwe T A. Controlled clinical trial of artemether (qinghousu derivative) versus quinine in complicated and severe falciparum malaria. *Trans R Trop Med Hyg* 1987; 81 : 559-61.

van Hensbroke MB, Onyiorah E, Jaffar S, *et al.* A trial of artemether or quinine in children with cerebral malaria. *N Engl J Med* 1996; 335 : 69-75.

Sharp D. Malarial range set to spread in a warmer world. *Lancet* 1996; 347 : 1612.

WHO. The development of artemisinin and its derivatives : Fifth meeting of the scientific working group on the chemotherapy of malaria. Geneva, October 6-7, 1986, Document, TDR/Chemal-SWG/Art 86.3.