

## CLINICAL TRIAL OF $\beta$ -ARTEETHER VERSUS QUININE FOR THE TREATMENT OF CEREBRAL MALARIA IN CHILDREN IN YAOUNDE, CAMEROON

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**Abstract.** One hundred and two children aged 0–10 years with cerebral malaria (Blantyre coma score of 2 or less) were randomly treated either with intramuscular arteether (3.2 mg/kg on Day 0, followed by 1.6 mg/kg on Days 1 to 4) or intravenous (IV) quinine dihydrochloride (20 mg of the salt/kg, followed by 10 mg of the salt/kg every 8 hr up to Day 6). Treatment with oral quinine sulfate (10 mg/kg every 8 hr) was substituted for IV quinine when the patient was able to take oral medicine. All patients were followed up in the hospital for 7 days; thereafter, they were treated as outpatients on Days 14, 21, and 28.

Mortality rate, the main efficacy parameter, was 11.8% lower in the arteether treatment group than in the quinine group (15.7% versus 27.4%); however, the difference was not significant ( $P = 0.25$ ). Means for fever clearance time, coma resolution time, and parasite clearance time were similar in the 2 treatment groups ( $42.2 \pm 34.9$  hr;  $34.8 \pm 18.8$  hr, and  $46.3 \pm 28.5$  hr, respectively for arteether, versus  $45.0 \pm 26.7$  hr;  $30.3 \pm 18.9$  hr, and  $40.7 \pm 18.9$  hr, respectively, for quinine). At 28 days, the cure rates were 73.2% and 64.9% for the arteether and quinine treatment groups, respectively.

Arteether is safe and therapeutically at least as effective as quinine for the treatment of cerebral malaria in children in Cameroon. Because of its ease of administration, arteether appears to be suited for use in the rural zones where monitoring facilities do not exist.

### INTRODUCTION

Parenteral quinine is the most widely-used treatment for severe and complicated malaria. Because of the emergence of multidrug resistance, its effectiveness is declining in some areas of the world, particularly in southeast Asia, but also in Africa,<sup>1–4</sup> necessitating the search for alternative drugs. Artemisinin derivatives appear to be the most promising new antimalarials. Patients with severe malaria who were treated with either intramuscular Artemether or intravenous (IV) quinine showed no significant differences in survival rate and parasite clearance time.<sup>5–7</sup> In 1985, arteether, a semisynthetic  $\beta$ -ethyl-ether derivative of artemisinin, was developed by the Walter Reed Army Institute of Research (WRAIR), in collaboration with the Unity Nation Development Program (UNDP), the World Bank, the World Health Organization (WHO)/Special program for Research and training in Tropical Diseases (TDR), the Dutch Ministry of Development Cooperation, and the Artecef/Beheer Besloten Venootschap Company, Maarssen, The Netherlands.

Preclinical phase I and II studies have shown that arteether could also be an alternative drug for the treatment of cerebral malaria in zones where *Plasmodium falciparum* appears to have reduced sensitivity or resistance to quinine.<sup>8–10</sup> A multicenter hospital-based study has been initiated by WHO to compare the efficacy of intramuscular arteether with the standard IV quinine (with loading dose) in the treatment of cerebral malaria in children in various malarial zones. The Medical Research Center in Yaounde, Cameroon, was chosen to be one of the sites for the trial.

### PATIENTS AND METHODS

**Study area.** The study was carried out from November 1995 to December 1997 in Yaounde, the capital of Cameroon, an area characterized by perennial transmission of ma-

laria throughout the year. However, there are peaks in transmission, which usually occur at the beginning of the rainy seasons (March to April and October to November).

The center for the recruitment, treatment, and management of patients was the pediatric ward of the Yaounde Central Hospital. This hospital receives patients from the town (1.5 million inhabitants) and from surrounding areas up to 50 km. The parasitological and other biological tests were performed at the Cameroon Medical Research Center, situated 5 km from the Yaounde Central Hospital.

**Recruitment and treatment of patients.** Patients were recruited from the population of children presenting at the hospital with cerebral malaria. Included in the study were boys and girls aged 0–10 years who had asexual *P. falciparum* parasitemia, a Blantyre coma score (BCS) of 2 or less, and no other obvious cause of coma. Excluded from the study were children presenting with chronic illness e.g., renal or liver diseases, frank acquired immune deficiency syndrome (AIDS), epilepsy, and cardiovascular accident/stroke. Children taking cardioactive drugs and those with a history of blackwater fever were also excluded. Patients were withdrawn from the study in case of a positive blood culture for a pathogen or of a positive cerebrospinal fluid test result (white cells  $> 5/\mu\text{L}$ , protein concentration  $> 30$  mg/100  $\mu\text{L}$ , or bacteria on gram stain or on culture). Parents or guardians gave informed consent, and ethical approval was given by the Cameroon National Ethics Committee.

On Day 0 and prior to the administration of any drug, the following parameters were determined: clinical history, physical and neurological examination, Blantyre coma score, *P. falciparum* parasitemia, full blood count, blood chemistry, blood culture for bacterial pathogen, and lumbar puncture (cell count, protein, gram stain, and culture).

Patients received either arteether (AE) or quinine (Q) according to a computer-generated randomization schedule.

TABLE 1  
Clinical and biological features at admission for the 2 treatment groups; figures in parentheses are standard deviations

Feature	Arteether group (n = 51)	Quinine group (n = 51)
Mean age (mo)	41.1	39
<b>Clinical</b>		
Ratio of boys to girls	26/25	23/18
Blantyre coma score (n)		
0	1	3
1	18	21
2	32	27
Patients with convulsions (n)	49	47
Rectal temperature (°C)	38.9 (1.1)	38.9 (1)
Pulse rate (beats/min)	146 (24.6)	147 (22.2)
Respiration rate (per min)	43.7 (10.9)	47.5 (14.0)
Blood pressure, systolic/diastolic	100.1/61.5 (14.0/8.7)	93.7/53.9 (16.2/13.9)
<b>Biological</b>		
Parasitemia (per $\mu$ l)	58,056 (75,479)	116,239 (201,415)
Packed cell volume (%)	27.6 (7.1)	30.7 (8.8)
Platelets (per $\mu$ l)	140,653 (60,925)	142,261 (79,887)
White blood cells (per $\mu$ l)	14,716 (13,356)	12,099 (5,134)
Red blood cells (per $\mu$ l)	$3.5 \times 10^6$ (0.7 $\times 10^6$ )	$3.8 \times 10^6$ (0.9 $\times 10^6$ )
Blood glucose (g/L)	0.8 (0.3)	0.7 (0.1)
Blood creatinine (mg/dl)	10.8 (13.2)	10.2 (13.5)
Blood urea (g/L)	0.6 (0.8)	0.6 (0.5)
Alanine aminotransferase (UI/L)	133.5 (354.8)	56.8 (58.4)
Aspartate aminotransferase (UI/L)	32.9 (39.1)	71.23 (178.3)

Arteether was given by intramuscular injection of 3.2 mg/kg on Day 0, followed by 1.6 mg/kg daily on Days 1 to 4. Quinine dihydrochloride (20 mg salt/kg) was infused intravenously over 4 hr (loading dose) followed by 10 mg salt/kg every 8 hr, infused over 2 hr up to Day 6. Treatment with oral quinine sulfate (10 mg salt/kg every 8 hr) was substituted for the IV quinine when the patient was able to take oral medicine and had received a minimum of 3 IV doses.

Recrudescent cases were treated with sulfadoxine-pyrimethamine (250 mg sulfadoxine-12.5 mg pyrimethamine per 10 kg). Common complications of cerebral malaria (hyperpyrexia, seizures, life threatening anemia) were managed according to the guidelines published by Warrel and others.<sup>11</sup>

**Follow-up of patients.** Patients were followed in the hospital for 7 days. On Day 7, they were discharged from the hospital and accompanied to their homes by the study driver in order to locate their homes for subsequent clinical and biological follow-up on Days 14, 21, and 28. In hospital, observations were made and recorded every 4 hr (pulse, respiratory rate, BCS) or every 8 hr (rectal temperature, blood pressure, *P. falciparum* parasitemia) until Day 7 and then upon discharge, weekly on Days 14, 21, and 28. On Days 0, 3, 7, 14, and 28, blood samples were taken for hematology and clinical chemistry tests. Physical and neurological examinations were done twice daily until Day 7, and thereafter weekly, on Days 14, 21, and 28.

Parasites were counted against 200 white blood cells (WBC) on thick blood film stained with Giemsa's solution. Parasites per microliter were calculated from each patient's most recent WBC count. A film was considered negative if no malaria parasite was detected after a minimum of 200 microscope oil fields were examined. Full blood count using a Coulter counter ACT 8 machine (Coulter Corporation, Miami, FL), included hemoglobin, red blood cells, platelets,

hematocrit, and reticulocytes. Blood chemistry using a Biomerieux spectrophotometer (BioMerieux, Paris, France) included total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, creatinine, urea, total protein, and glucose.

**Statistical analysis.** Statistical analysis was performed with Epi-Info software, 5.0 version. Comparison of groups with normally distributed data was made by analysis of variance after application of Bartlett's test for homogeneity of variance and proportion by the Fisher exact test and the chi-square test. *P*-values < 0.05 were considered statistically significant.

## RESULTS

**Study population.** One hundred and six patients were initially enrolled in the study; 2 of them (AE group) dropped out, 1 before and the other after Day 7. Therefore, they were excluded from the calculation of the 28-day cure rate; however, they were included in the calculation of other efficacy parameters such as parasite clearance time (PCT), fever clearance time (FCT), and coma resolution time (CRT). Four patients were excluded from the calculation of all the parameters (2 for sepsis and 2 for unusually rapid recovery of consciousness, which cast doubt on the diagnosis of cerebral malaria). Finally, 102 patients (51 in each group) were included in the analysis of the different indicators of treatment response. Their ages ranged from 6 to 108 months (mean = 39.6). The sex ratio (boys to girls) was 59:43.

**Baseline parameters.** The admission clinical and biological characteristics of patients in the 2 treatment groups are shown in Table 1. Means for ALT, blood sugar, and WBC were significantly higher in the AE group than in the Q group. On the contrary, means for AST, RBC, parasitemia,

TABLE 2

Mortality rate according to treatment received and to initial Blantyre coma score; figures in parentheses represent number of deaths\*

	Blantyre coma score (deaths)			Total score (0 + 1 + 2)
	0	1	2	
AE	1 (1)	18 (5)	32 (2)	51 (8)
Q	3 (1)	21 (11)	27 (2)	51 (14)
AE + Q	4 (2)	39 (16)	59 (4)	102 (22)
Mortality rate (%)	50.0	41.0	6.8	21.6

\* AE = arteether group; Q = quinine group.

and respiratory rate were significantly higher in the Q group. The other baseline parameters showed no significant differences in the 2 treatment groups.

**Serious adverse events.** In the AE group, no serious side effects were reported. In the Q group, one 13-month-old patient who was receiving quinine therapy for only the second time (having received quinine the first time at the age of 9 months without reaction) presented with fatal blackwater fever following quinine administration. The death occurred 12 hr 45 min post-treatment even though quinine administration was stopped and a blood transfusion was done.

**Outcome of disease and recovery times.** *Mortality rate.* There was an overall mortality rate (MR) of 21.6%, with 15.7% (8/51) in the AE group and 27.4% (14/51) in the Q group ( $P = 0.25$ ). As shown in Table 2, independent of the treatment received, the initial BCS seemed to influence the outcome of the disease. Of the 43 children who presented with a BCS of 0 or 1, 18 (41.9%) died whereas only 4 (6.8%) died out of the 59 who presented with an initial BCS of 2 ( $P = 0.442$ ). Death usually occurred within the first 24 hr following the initiation of the treatment (75.0% and 78.6% in the AE and Q groups, respectively).

*Coma resolution time.* Among the survivors, mean CRTs were 34.8 hr versus 30.3 hr respectively for the AE and Q treatment groups (Table 3). The difference in CRT was not significant ( $df = 1-78$ ;  $F = 1.144$ ).

*Fever clearance time.* Two patients in the AE group and 1 patient in the Q group were afebrile throughout the study. Two other patients in the AE group had concomitant infections necessitating antibiotic treatment. These 5 children were not included in the calculation of FCT. Mean FCT was 42.2 hr for the AE group and 45.0 hr for the Q group. Here also, the difference was not significant ( $df = 1-76$ ;  $F = 0.150$ ).

*Parasite clearance time and 28-day follow-up.* Parasite clearance time was higher in the AE group than in the Q group (46.3 versus 40.7 hr), but the difference was not significant ( $df = 1-78$ ;  $F = 1.058$ ); 41 patients in the AE group (80.4%) and 37 in the Q group (72.5%) completed the 28-day follow-up. One patient in the AE group (2.4%) and 5 in the Q group (13.5%) had an RII type of response (the parasitemia had not cleared by Day 7) and 10 children in the AE group (24.4%) and 8 in the Q group (21.6%) had recrudescence or possibly reinfection between Day 7 and Day 28 (an RI type of response). The second malaria episode occurred on either Day 21 (7/8 patients with an RI type of response in the Q group versus 5/10 in the AE group) or on Day 28 (1/8 children in the Q group versus 5/10 in the AE

TABLE 3

Recovery times and outcomes\*

Parameter	Arteether group	Quinine group
<b>PCT (hr)</b>		
Patients included in calculation (n)	43	37
Mean (SD)	46.3 (28.5)	40.7 (18.9)
<b>CRT (hr)</b>		
Patients included in calculation (n)	43	37
Mean (SD)	34.8 (18.8)	30.3 (28.9)
<b>FCT (hr)</b>		
Patients included in calculation (n)	39	36
Mean (SD)	42.2 (34.9)	45.0 (26.7)
Deaths (n)	8	14
Mortality rate (% and proportion)	15.7 (8/51)	27.4 (14/51)
<b>Survivors</b>		
Total (n)	43	37
Full recovery (n)	39	36
Survived with sequelae (n)	2	1
Lost to follow-up (n)	2	0
28-day cure rate (% and proportion)	73.2 (30/41)	64.9 (24/37)

\* PCT = parasite clearance time; CRT = coma resolution time; FCT = fever clearance time.

group). Finally, the 28-day cure rate was 73.2% for AE-treated patients and 64.9% for the Q-treated ones.

*Follow-up of other parameters.* The pattern in the evolution of hematological, biochemical, and other clinical parameters during the follow-up period was similar in the 2 treatment groups in spite of the differences observed in some baseline parameters at admission.

## DISCUSSION

The mortality rate, the primary efficacy parameter, was similar in the 2 treatment groups. Independent of the treatment received, mortality in children with cerebral malaria is usually 10–40%.<sup>2</sup> Mortality rate in our 2 treatment groups remained within that range. The initial BCS seemed to influence the mortality rate, with the highest MR occurring in the lowest BCS groups. On the contrary, there was no relationship between the initial parasitemia or the initial temperature and the MR. These findings are consistent with the results of many authors who have worked with artemisinin derivatives.<sup>5–8</sup> In some cases, significant rapid CRT and PCT have been noted in children treated with  $\beta$ -artemether compared with those treated with quinine.<sup>12</sup> Like many authors who have studied artemether,<sup>8,12,13</sup> we noted longer FCT in patients treated with quinine (45.0 hr) than in those treated with AE (42.2 hr). On the contrary, we had longer PCT in the AE treatment group (46.3 hr) than in the Q group (40.7 hr), the opposite of findings in the previously mentioned studies. In any case, the differences between the PCT and FCT recovery times in the 2 treatment groups were not significant.

In our study, 41 children in the AE group and 36 in the Q group completed the 28-day follow-up. Among them, 24.4% in the AE group and 21.6% in the Q group had an RI type of response. Even though delayed recrudescence has been reported after treatment with artemisinin derivatives,<sup>14</sup> because Yaounde is a zone of perennial malaria transmission, we cannot say whether these cases were due to rein-

fection or to delayed recrudescence. One case of the RII type of response was noted in an AE receiver. Studies in Kenya have shown that some children, especially those with respiratory distress, absorb intramuscular artemether poorly.<sup>13</sup> This may also occur with arteether and could explain the RII type of response noted with this drug. The possibility that quinine-resistant strains of *P. falciparum* are present in Yaounde cannot be excluded, because the phenomenon has already been described *in vitro* from the sahel part of Cameroon.<sup>1</sup> In any case, blood samples were taken from patients at the time of recrudescence and sent to WRAIR for *in vitro* drug sensitivity tests and drug dosages. The results are pending.

The activities of  $\beta$ -artemether and  $\beta$ -arteether are comparable.<sup>9</sup> Because of their ease of administration, they are suited for use in rural zones, where monitoring facilities are most often absent. Arteether has advantages over artemether. It is more lipophilic and can accumulate easily in brain tissues, which is advantageous in cerebral malaria patients. The  $\beta$ -anomer of AE, a crystalline solid, is the predominant anomer upon synthesis and is easy to separate from the  $\alpha$ -anomer, which is a liquid, so that there is the potential for large-scale production.<sup>8,9</sup> Finally, because of this and because AE was manufactured jointly by WHO and other partners, it is likely to cost less than artemether.

In conclusion, AE is safe, well tolerated, and as effective as quinine for the treatment of cerebral malaria in children in Yaounde, Cameroon. In addition, it is easy to use. Therefore, it appears to be a promising alternative drug for the treatment of severe and complicated malaria in areas of quinine resistance and in rural zones where monitoring facilities are usually absent.

**Acknowledgments:** We are grateful to Dr. David E. Davidson of Damascus, MD; to Dr. Charles B. Lugt of the Artecef/Beheer Besloten Vennootschap Company, Maarssen, The Netherlands, for their support throughout this study; and to the medical staff of the pediatric ward of Yaounde Central Hospital for their cooperation.

**Financial support:** This study received financial support from the Unity Nation Development Program/World Bank/World Health Organization Special program for Research and Training in Tropical Diseases (950420).

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