

# The New England Journal of Medicine

© Copyright, 1996, by the Massachusetts Medical Society

VOLUME 335

JULY 11, 1996

NUMBER 2



## A TRIAL OF ARTEMETHER OR QUININE IN CHILDREN WITH CEREBRAL MALARIA

MICHAËL BOELE VAN HENS BROEK, M.D., EMEKA ONYIORAH, M.D., SHABBAR JAFFAR, M.Sc., GISELA SCHNEIDER, M.D., AYO PALMER, M.D., JOOST FRENKEL, M.D., GODWIN ENWERE, M.D., SABINE FORCK, M.D., ANNE LIESE NUSMEIJER, M.D., STEVE BENNETT, Ph.D., BRIAN GREENWOOD, M.D., AND DOMINIC KWIATKOWSKI, M.D.

### ABSTRACT

**Background** Cerebral malaria has a mortality rate of 10 to 30 percent despite treatment with parenteral quinine, a situation that may worsen with the spread of quinine resistance. Artemether is a new antimalarial agent that clears parasites from the circulation more rapidly than quinine, but its effect on mortality is unclear.

**Methods** We conducted a randomized, unblinded comparison of intramuscular artemether and intramuscular quinine in 576 Gambian children with cerebral malaria. The primary end points of the study were mortality and residual neurologic sequelae.

**Results** Fifty-nine of the 288 children treated with artemether died in the hospital (20.5 percent), as compared with 62 of the 288 treated with quinine (21.5 percent). Among the 418 children analyzed at approximately five months for neurologic disease, residual neurologic sequelae were detected in 7 of 209 survivors treated with artemether (3.3 percent) and 11 of 209 survivors treated with quinine (5.3 percent,  $P=0.5$ ). After adjustment for potential confounders, the odds ratio for death was 0.84 (95 percent confidence interval, 0.53 to 1.32) in the artemether group, and for residual neurologic sequelae, 0.51 (95 percent confidence interval, 0.17 to 1.47). There were fewer local reactions at the injection site with artemether than with quinine (0.7 percent vs. 5.9 percent,  $P=0.001$ ).

**Conclusions** Artemether is as effective as quinine in the treatment of cerebral malaria in children. (N Engl J Med 1996;335:69-75.)

©1996, Massachusetts Medical Society.

**A**BOUT half a million African children die each year as a result of cerebral malaria. The recommended therapy is parenteral quinine, but the case fatality rate is 10 to 30 percent despite treatment.<sup>1,2</sup> Quinine has several other limitations. Because of its potential toxicity it is ideally administered by carefully controlled intravenous infusion — a procedure that is often impractical in rural health clinics, especially in young children. Under these circumstances, the World Health Organization recommends administration by the intramuscular route,<sup>3</sup> which is equally effective in terms of parasite clearance but tends to produce irritation and, infrequently, abscess formation at the site of injection.<sup>4</sup> Of increasing concern is the declining efficacy of quinine in parts of Southeast Asia,<sup>5</sup> a trend that could prove disastrous if it spreads to Africa, where most deaths from malaria occur. Thus, there is an urgent need to identify new forms of therapy for severe malaria that are economical and practical alternatives to quinine and, ideally, improve the clinical outcome of cerebral malaria.

Among potential alternatives to quinine, the artemisinin (qinghaosu) derivatives have attracted special interest because of the rapidity with which they reduce *Plasmodium falciparum* parasitemia.<sup>6</sup> Artemether, the methyl ether of dihydroartemisinin (the

From Medical Research Council Laboratories, Fajara (M.B.H., E.O., S.J., B.G.); Sibanor Health Centre, Sibanor (G.S., S.F.); and the Department of Paediatrics, Royal Victoria Hospital, Banjul (A.P., G.E.) — all in the Gambia; the Departments of Tropical Medicine (M.B.H.) and Pediatrics (J.E., A.N.), University of Amsterdam, Academic Medical Center, Amsterdam; the Department of Epidemiology and Population Sciences, London School of Hygiene and Tropical Medicine, London (S.B.); and the University Department of Paediatrics, John Radcliffe Hospital, Oxford, United Kingdom (D.K.). Address reprint requests to Dr. Boele van Hensbroek at the Department of Tropical Medicine F4, Academic Medical Center, Meibergdreef 9, 1105AZ Amsterdam, the Netherlands.

active metabolite of artemisinin), is formulated as an intramuscular injection that has been shown in several clinical studies to clear parasites more quickly than quinine.<sup>6</sup> In addition, a study in Malawi reported that children with cerebral malaria recovered more quickly from coma when treated with artemether than when treated with quinine.<sup>7</sup> These and other promising findings have led to the widespread, but so far unproved, belief that artemether may reduce the rate of death from cerebral malaria. Thus, we compared the ability of artemether and quinine to prevent death or neurologic sequelae in children with cerebral malaria.

## METHODS

### Study Population

The study was conducted in the Gambia, West Africa, between 1992 and 1994. Recruitment began at the Royal Victoria Hospital in Banjul, which is the chief referral hospital for the western part of the country. In 1993, the study was extended to include Sibanor Health Centre, a mission hospital 90 km from Banjul that serves as a primary and secondary health care facility for a mainly rural population. Unconscious children one to nine years of age who were brought to Royal Victoria Hospital or Sibanor Health Centre were eligible for the study if they had a Blantyre coma score of 2 or less,<sup>8</sup> asexual forms of *P. falciparum* were identified on a thick blood film, and a parent or guardian gave informed consent. To confine recruitment to patients with true cerebral malaria, patients with diseases other than malaria at the time of admission were excluded, as were those who recovered consciousness immediately after the correction of hypoglycemia or within one hour if they were convulsing on admission. Those treated with quinine before admission were also excluded; no child had previously received artemether.

### Study Design

Intramuscular artemether and intramuscular quinine were compared in an open, randomized trial that was part of a larger trial of cerebral-malaria intervention, in which a monoclonal antibody against tumor necrosis factor (TNF) was also evaluated. A two-by-two factorial design was used to allow artemether to be compared with quinine while anti-TNF therapy was compared with placebo in the same group of patients. The statistical principles of factorial design are well established.<sup>9,10</sup>

The treatment code for each child was stored in a sealed envelope that was opened after the admission procedure was completed and parental consent had been obtained. To ensure that disease severity was well matched between the treatment groups, randomization was stratified according to the coma score at admission (0, 1, or 2) and the study center and was balanced over time in blocks of 10 for both antimalarial and anti-TNF therapy. The different dose schedules used for artemether and quinine meant that the ward staff members were aware of the patients' treatment assignments. However, the assessment of neurologic sequelae in survivors was carried out by a doctor who was unaware of the treatment code. In addition to the randomization for artemether and quinine, each child was also assigned to receive either anti-TNF therapy (5 mg per kilogram of body weight) or placebo, given as a double-blinded intravenous dose. The randomization procedure ensured that anti-TNF therapy and placebo were evenly distributed between the quinine and artemether groups.

The primary end points of the study were death in the hospital and residual neurologic sequelae that persisted when the child was assessed during the dry season following the illness. The secondary end points were rates of clearance of parasites and fever, length of time to recovery from coma, and neurologic sequelae

at discharge and one month after admission. The sample size was determined at the outset, to provide an 80 percent probability of detecting a 33 percent reduction in mortality at the 5 percent significance level. These estimates were based on our previous experience of a 25 to 30 percent mortality rate in this group of patients and on data from Southeast Asia suggesting that artemether might reduce mortality by up to 50 percent.<sup>6</sup>

### Antimalarial-Treatment Schedules

Patients assigned to the artemether group received intramuscular injections of artemether (Paluther, Rhône-Poulenc Rorer, Vitry-sur-Seine, France) in the anterior thigh for four days, in an initial dose of 3.2 mg per kilogram, followed by daily doses of 1.6 mg per kilogram. Those assigned to the quinine group received intramuscular injections of quinine dihydrochloride (Rotexmedica, Trittau, Germany) in the anterior thigh for five days, in an initial dose of 20 mg per kilogram, followed by a dose of 10 mg per kilogram every 12 hours. Because of the irritant effect of intramuscular quinine, its concentration was diluted to 60 mg per milliliter and the initial dose divided between thighs. Once a patient was able to swallow, intramuscular injections were replaced by oral quinine sulfate. With the above regimens, it was found in the first year of the study that recrudescence of parasitemia was relatively common in both treatment groups at one month of follow-up. In the second and third years of the study, to reduce the rate of recrudescence, pyrimethamine-sulfadoxine (Fansidar, Hoffmann-LaRoche, Reinach, Switzerland) was added to the antimalarial treatment regimen in both groups, in a dose as close as possible to one of 1.25 mg of pyrimethamine per kilogram and 25 mg of sulfadoxine per kilogram orally. Pyrimethamine-sulfadoxine was given only after a child had fully regained consciousness and after parasitemia and fever had cleared, to avoid affecting the secondary end points of the study.

### Clinical Assessment and Management

On admission, the patient's history and clinical findings were recorded on standardized forms. A venous blood sample was obtained for preparation of a thick blood film, estimation of the blood glucose level (with Haemoglucotest 1-44 R strips and a Reflux S meter, Boehringer Mannheim, Livingston, United Kingdom), for the determination of packed-cell volume, and for blood culture, hematologic analysis, and biochemical analysis. Hypoglycemia, defined as a blood glucose level below 40 mg per deciliter (2.2 mmol per liter), was treated immediately with 1 ml of 50 percent glucose per kilogram intravenously. Convulsions were treated initially with diazepam (0.5 mg per kilogram rectally or 0.3 mg per kilogram intravenously), followed if necessary by paraldehyde (0.1 ml per kilogram). Children with repeated or refractory convulsions received phenobarbital (15 mg per kilogram intramuscularly). Lumbar puncture was performed, unless clinically contraindicated, to rule out meningitis. Fluids (4 percent glucose in 0.18 percent saline solution) were given intravenously to comatose patients. The packed-cell volume was measured daily, and a blood transfusion (15 ml per kilogram) was given if it fell below 15 percent. Cases of secondary infection (primarily aspiration pneumonia) were treated with chloramphenicol. Vital signs (including temperature, pulse, respiratory rate, and coma score) were recorded every 4 hours for the first 24 hours and then every 6 hours until discharge. Blood glucose measurements were repeated after 4 and 12 hours and when clinically indicated. At the Royal Victoria Hospital, blood films were examined every 12 hours and the number of asexual parasites per 200 white cells (thick film) or 1000 red cells (thin film) was counted in order to determine the level of parasitemia. Each blood film was examined by two independent observers who were unaware of the treatment code. Data on admission characteristics, primary end points of the study, and time to recovery from coma were recorded at both study centers. Sequential observations on the clearance of parasites and resolution of fever were made only at Royal Victoria Hospital.

Each child underwent a physical examination with neurologic

assessment at the time of discharge. A child was considered to have neurologic sequelae if he or she had any of the following neurologic abnormalities: paresis, ataxia, spasticity, floppiness, hearing defects, visual-field defects, aphasia, behavioral abnormalities, or developmental regression. All surviving children were asked to return one month after admission, for a further detailed neurologic assessment by a clinical investigator. This included a questionnaire on the child's behavior and performance and a detailed examination. Those who had neurologic sequelae at one month were reviewed by the same clinical investigator during the following dry season, approximately five months after admission. Those without evident sequelae at one month were visited by a field worker, and if there was any doubt about their health or performance, they were referred to the clinical investigator for further evaluation. Ninety-five percent of the survivors were reexamined one month after admission, and 92 percent approximately five months after admission. In both treatment groups a similar proportion of patients was lost to follow-up, most often because of emigration from the Gambia or an incorrect address.

**Statistical Analysis**

The protocol specified two initial procedures to be completed before a full analysis of the data was undertaken. First, because of the factorial design, it was necessary to examine whether randomization to the group receiving anti-TNF therapy or placebo might have affected any difference in results between artemether and quinine. Second, we used a multiple logistic-regression model, omitting treatment as a variable, to identify admission variables that were related to clinical outcome and that were potential confounders. In the case of death, these were temperature, pulse rate, the presence of hypoglycemia at admission, coma score, and study center; in the case of neurologic sequelae, they were duration of coma, coma score, and the presence of hypoglycemia at admission. In analyzing the effect of antimalarial treatment, and specifically when determining odds ratios, we used a multiple logistic-regression model to correct for these potential confounders, as well as for any possible effect of anti-TNF therapy on the primary outcome measures.

Discrete data were analyzed by the chi-square test or Fisher's exact test, with stratified analysis by the Mantel-Haenszel test and multivariate analysis by unconditional logistic regression. Continuous secondary end points that were normally distributed were analyzed by Student's t-test, after the application of Bartlett's test for homogeneity of variance; those that were not normally distributed were analyzed by the Wilcoxon test. Survival was compared with use of Kaplan-Meier plots and the log-rank test, with multivariate analysis by Cox regression. Different multivariate models were compared with the likelihood-ratio test.

The study was approved by the Gambian Government-Medical Research Council Laboratories Ethics Committee. The study was monitored by the Tropical Disease Research Program of the World Health Organization, and the major outcome measures were reviewed annually by an independent monitoring committee. A coded data base and detailed analytic plan were submitted to the monitoring committee before the blinded randomization codes were broken at the end of the study. The results presented follow that analytic plan.

**RESULTS**

**Clinical Features on Admission**

A total of 576 children were randomly assigned to receive artemether or quinine, 341 at Royal Victoria Hospital and 235 at Sibanor Health Centre. Three children who died after randomization but before treatment could be given were excluded. The clinical features on admission were similar in the two groups (Table 1). Over half of the children had a history of recent chloroquine treatment, and 39 percent had a

clinically notable plasma level of chloroquine (>100 ng per milliliter), but these features were unrelated to outcome. On admission, 24 percent had hypoglycemia and 8 percent had severe anemia (packed-cell volume <15 percent, or hemoglobin <5 g per deciliter).

**Primary End Points**

**Mortality**

Fifty-nine of the 288 children treated with artemether died in the hospital (20.5 percent), as compared with 62 of the 288 children treated with quinine (21.5 percent, P=0.8) (Table 2). The adjusted odds ratio for death among the children in the artemether group was 0.84 (95 percent confidence interval, 0.53 to 1.32). An intention-to-treat analysis, which included the three children who died before treatment was given, did not alter the odds ratio. As shown in Figure 1, the length of time to death was similar in the artemether group (median, 11 hours; interquartile range, 5 to 25) and the quinine group (median, 13 hours; interquartile range, 5 to 26; P=0.8 by the log-rank test). One child in the quinine group, who was well at the time of discharge, died at home four days later.

**Sequelae**

Neurologic assessment was carried out during the dry season in 418 of the 454 survivors (92 percent),

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS ACCORDING TO TREATMENT ASSIGNMENT.\***

CHARACTERISTIC	ARTEMETHER (N=288)	QUININE (N=288)
Female sex (%)	47.2	50.5
Age (mo)	48.0±21.6	46.0±21.4
Duration of coma (hr)		
Median	6.0	6.0
Range	1-150	1-96
Prior chloroquine treatment (%)	55.8	59.3
Temperature (°C)	38.8±1.1	38.8±1.0
Pulse rate (per minute)	147±23.0	145±22.5
Respiration rate (per minute)	51±15.1	50±13.5
Coma score (%)		
0	22.2	20.5
1	31.6	31.9
2	46.2	47.6
Hypoglycemia (%)†	26.3	22.3
Degree of parasitemia (geometric mean count/mm <sup>3</sup> )	57,106	55,471
Hemoglobin (g/dl)	8.1±2.6	8.4±2.5
Severe anemia (%)‡	8.7	8.1

\*Plus-minus values are means ±SD.

†Hypoglycemia was defined as a blood glucose level below 40 mg per deciliter (2.2 mmol per liter).

‡Severe anemia was defined as a packed-cell volume below 15 percent or a hemoglobin concentration below 5 g per deciliter.

**TABLE 2. MORTALITY AND INCIDENCE OF NEUROLOGIC SEQUELAE AMONG CHILDREN TREATED FOR CEREBRAL MALARIA WITH ARTEMETHER OR QUININE.\***

VARIABLE	ARTEMETHER	QUININE	CRUDE ANALYSIS		ADJUSTED ANALYSIS†	
			ODDS RATIO (95% CI)	P VALUE	ODDS RATIO (95% CI)	P VALUE
	no./total no. (%)					
Primary end point						
Death in the hospital‡	59/288 (20.5)	62/288 (21.5)	0.94 (0.62–1.43)	0.8	0.84 (0.53–1.32)	0.5
Residual neurologic sequelae§	7/209 (3.3)	11/209 (5.3)	0.62 (0.21–1.78)	0.5	0.51 (0.17–1.47)	0.2
Secondary end point						
Neurologic sequelae at discharge	48/229 (21.0)	57/226 (25.2)	0.79 (0.50–1.25)	0.3	0.81 (0.50–1.31)	0.4
Neurologic sequelae at 1 month§	18/218 (8.3)	21/214 (9.8)	0.83 (0.41–1.68)	0.7	0.78 (0.39–1.58)	0.5

\*CI denotes confidence interval.

†In the analysis of mortality the values were adjusted for temperature, pulse rate, presence of hypoglycemia, coma score, study center, and anti-TNF-therapy status. In the analysis of neurologic sequelae values were adjusted for the duration of coma before admission, presence of hypoglycemia, coma score, and anti-TNF-therapy status.

‡Data on one child in the quinine group, who died at home four days after discharge, were excluded.

§One month after admission, 95.2 percent of surviving children returned for neurologic assessment (433 of 455); approximately five months later, during the dry season, 92.1 percent (418 of 454) returned for assessment of any residual sequelae.

an average of five months (range, three to nine) after admission. Residual neurologic sequelae were detected in 7 of 209 survivors who had received artemether (3.3 percent), as compared with 11 of 209 of those treated with quinine (5.3 percent). This difference was not statistically significant ( $P=0.5$ ). The adjusted odds ratio for residual sequelae for children in the artemether group was 0.51 (95 percent confidence interval, 0.17 to 1.47).

Because of the factorial design, we examined whether the differences between artemether and quinine were the same for children treated with anti-TNF as for those who received placebo. Among children treated with artemether, there were 24 deaths in the anti-TNF group ( $n=138$ ), 30 in the placebo group ( $n=145$ ), and 5 in the group excluded from anti-TNF analysis ( $n=5$ ). Among those who received quinine, there were 32 deaths in the anti-TNF group ( $n=142$ ), 28 in the placebo group ( $n=140$ ), and 2 in the group excluded from anti-TNF analysis ( $n=6$ ). With respect to residual neurologic sequelae among survivors treated with artemether, there were 5 cases in the anti-TNF group ( $n=105$ ) and 2 in the placebo group ( $n=104$ ). Among survivors who received quinine, there were 8 cases of residual sequelae in the anti-TNF group ( $n=100$ ), 3 in the placebo group ( $n=105$ ), and none in the group excluded from anti-TNF analysis ( $n=4$ ). These data provide no evidence of an interaction between artemether and anti-TNF (chi-square value for the analysis of mortality, 0.75;  $P=0.4$ ; chi-square value for the analysis of neurologic sequelae, 0.018;  $P=0.9$ ). Furthermore, removing anti-TNF therapy from the

list of potential confounding variables caused little change in the adjusted odds ratios for mortality (odds ratio, 0.85; 95 percent confidence interval, 0.53 to 1.32) and neurologic sequelae (odds ratio, 0.49; 95 percent confidence interval, 0.17 to 1.43).

### Secondary End Points

#### Sequelae at Discharge and One Month

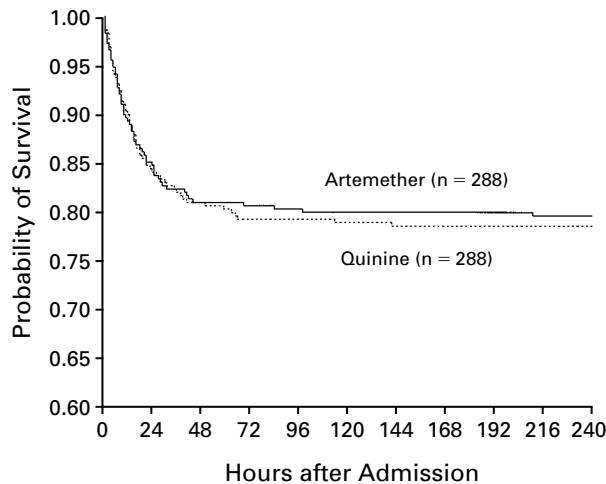
At the time of discharge, 21.0 percent of survivors in the artemether group and 25.2 percent in the quinine group had neurologic sequelae. At one month the proportions were 8.3 percent and 9.8 percent, respectively. Neither of these differences was statistically significant.

#### Recovery from Coma

Eleven of the 455 children who were discharged from the hospital did not fully regain consciousness; 6 had received artemether and 5 had received quinine. Among the 444 children who did recover from coma, the median recovery time was 26 hours among those treated with artemether and 20 hours among those treated with quinine ( $P=0.046$  by the Wilcoxon test) (Table 3). The probability of recovering from coma in the artemether and quinine groups, respectively, was 0.48 and 0.59 within 24 hours, 0.77 and 0.80 within 48 hours, and 0.91 and 0.88 within 72 hours.

#### Clearance of Parasites

The times needed for the parasite counts to fall by 50 percent and 90 percent of the admission value and to clear completely were significantly shorter in



**Figure 1.** Kaplan-Meier Analysis of Survival of 576 Children Treated for Cerebral Malaria with Artemether or Quinine.

Seventy-three percent of all deaths occurred within 24 hours after admission, and 91 percent within 48 hours. The hazard ratio for artemether was 0.99 (95 percent confidence interval, 0.84 to 1.17).

children treated with artemether than in those treated with quinine ( $P < 0.01$  for each comparison by the Wilcoxon test) (Table 3 and Fig. 2). In the first year of the study, 29.6 percent of the artemether-treated patients and 17.6 percent of the quinine-treated patients had parasitemia after one month of follow-up ( $P = 0.4$ ). In subsequent years, when pyrimethamine-sulfadoxine was given before discharge, the rates dropped to 10.6 percent for the artemether group and 9.4 percent for the quinine group.

**Clearance of Fever**

The time to clearance of fever, defined as the time needed for the rectal temperature to fall below 38.0°C for at least 24 hours, was 30 hours in the artemether group and 33 hours in the quinine group ( $P = 0.8$  by the Wilcoxon test) (Table 3 and Fig. 3).

**Complications of Cerebral Malaria**

Significantly more children in the artemether group than in the quinine group had convulsions after treatment began (38.5 percent vs. 28.1 percent,  $P = 0.01$ ). After adjustment for convulsions before the start of treatment and the duration of coma, the odds ratio was 1.86 (95 percent confidence interval, 1.28 to 2.71;  $P < 0.001$  by multiple logistic-regression analysis). Though not statistically significant, there was a greater tendency for hypoglycemia to occur after treatment with quinine than after artemether treatment (14.6 percent vs. 10.1 percent;  $P = 0.13$ ). After stratification according to the presence of hypoglycemia on admission, the odds ratio was 1.69 (95 percent confidence interval, 0.97 to

2.98;  $P = 0.07$  by the Mantel-Haenszel chi-square test). The two groups were similar in terms of other complications, including the extent of the fall in hemoglobin levels over a period of seven days, the need for blood transfusions, and the incidence of secondary bacterial infections (data not shown).

**Side Effects**

Local reactions at the site of the intramuscular injections were more common in the quinine-treated children than in the artemether-treated patients (5.9 percent vs. 0.7 percent,  $P = 0.001$ ). An abscess requiring incision and drainage developed in six children (five in the quinine group and one in the artemether group). One case of urticarial rash was observed in the quinine group.

**DISCUSSION**

Our results show that, in terms of preventing death or neurologic sequelae caused by cerebral malaria, artemether is about as effective as intramuscular quinine, the treatment currently recommended by the World Health Organization for tropical clinics with limited resources.<sup>3</sup> Artemether is a practical alternative to quinine, since it is less irritating when given intramuscularly and need be given only once a day.

Although parasites were cleared from the circulation significantly faster by artemether than by quinine (median time to decrease in the levels to 50 percent of the admission value, 9 hours vs. 14 hours;  $P = 0.005$ ), the fatality rate was similar for both drugs (20.5 percent vs. 21.5 percent). It had been widely anticipated that a more rapid reduction of parasitemia would bring about a corresponding reduction in mortality. Several smaller trials in Southeast Asian adults with various forms of severe malaria suggested that treatment with artemisinin derivatives might halve mortality.<sup>6</sup> In the context of childhood cerebral malaria in Africa, we found no significant difference in

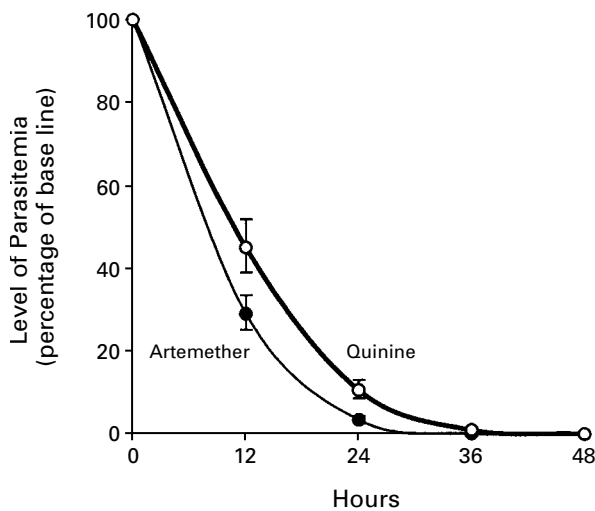
**TABLE 3.** LENGTH OF TIME TO CLEARANCE OF PARASITES, RESOLUTION OF FEVER, AND RECOVERY FROM COMA.

VARIABLE	ARTEMETHER	QUININE	P VALUE
	median (interquartile range)		
Time to parasite clearance (hr)			
Decrease to 50% of admission value	9 (7-16)	14 (7-21)	0.005
Decrease to 10% of admission value	22 (16-28)	25 (20-34)	0.008
Total clearance	48 (36-60)	60 (48-72)	<0.001
Time to resolution of fever (hr)			
Decrease in rectal temperature to <38°C	8 (4-16)	12 (4-12)	0.8
Maintenance of rectal temperature <38°C for at least 24 hr	30 (16-48)	33 (12-60)	0.8
Time to recovery from coma (hr)	26 (15-48)	20 (12-43)	0.046

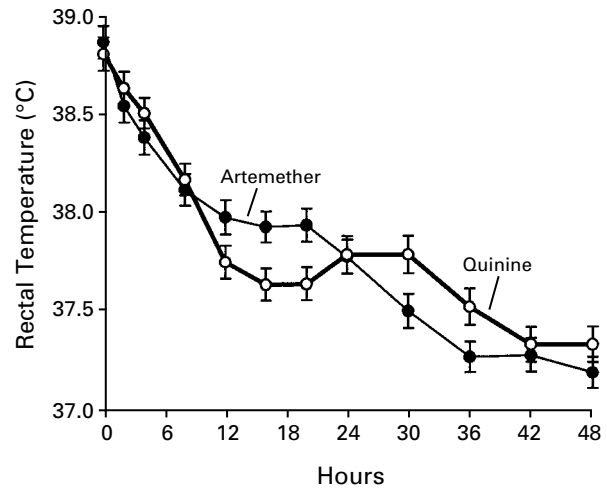
clinical outcome between patients given artemether and those given quinine, although the adjusted odds ratios had wide confidence limits and we cannot exclude the possibility that artemether would reduce mortality and sequelae if its use were widespread. Our study was carried out in a region where *P. falciparum* remains fully sensitive to quinine, and it is conceivable that the benefit of artemether would be greater in regions where quinine resistance occurs.

There has been concern that artemether may be neurotoxic at high doses. This has been observed in studies in animals given a dose of 15 mg per kilogram daily for 28 days, though it has yet to be demonstrated in humans.<sup>11</sup> Our finding of an increased incidence of convulsions in the artemether group, together with a tendency toward a longer time to recovery from coma, could conceivably be due to such an effect. But the data provide no evidence to suggest that long-term neurologic damage is caused by artemether at this dosage, since the incidence of neurologic sequelae tended to be lower after treatment with artemether than after treatment with quinine. The proportion of survivors with evident neurologic abnormalities at discharge was 21.0 percent in children treated with artemether and 25.2 percent in those who received quinine. It is encouraging to note that this rate fell considerably over the following three to nine months, to 3.3 percent and 5.3 percent, respectively.

A practical advantage of artemether is that it is considerably less likely than quinine to cause reactions at the site of intramuscular injection. In this study, such reactions occurred in 5.9 percent of children treated with intramuscular quinine despite the



**Figure 2.** Mean ( $\pm$ SE) Level of Parasitemia in Children Treated for Cerebral Malaria with Artemether or Quinine. The mean level of parasitemia was expressed as a percentage of the admission value.



**Figure 3.** Time to Resolution of Fever in Children Treated for Cerebral Malaria with Artemether or Quinine.

The mean ( $\pm$ SE) rectal temperature is shown for all patients except those in whom a secondary infection was diagnosed.

fact that we used a diluted formula of quinine (60 mg per milliliter). In most cases the problem was tenderness and induration at the injection site, which resolved within a few weeks, but in some children a sterile abscess developed that required incision and drainage. We also noted a tendency for hypoglycemic episodes to occur more often after treatment with quinine. Quinine is a potent stimulator of insulin secretion and a well-known cause of hypoglycemia in adults with falciparum malaria.<sup>12</sup> Previous studies in African children were unable to show a relation between quinine treatment and hypoglycemia, although 30 percent of Malawian children had mildly elevated insulin levels during a hypoglycemic episode.<sup>13,14</sup> Our findings suggest that quinine contributes to hypoglycemia in a proportion of children with cerebral malaria.

A disadvantage of both artemether and quinine is that they are relatively inefficient at eradicating infection.<sup>15,16</sup> In the first year of the study it became apparent that a large number of children who were apparently free of parasitemia at discharge had parasites in their blood at the one-month follow-up (30 percent of the artemether group and 18 percent of the quinine group). In the second and third years of the study, all children were given pyrimethamine-sulfadoxine at the end of the treatment period. To avoid affecting the study end points, this was done after the child had recovered from coma, fever, and apparent parasitemia. As a result, the proportion of survivors who had parasitemia at 28 days fell to approximately 10 percent in both the artemether and quinine groups. The latter figure may represent the underlying risk of acquiring a second infection.

A fundamental question arising from these data is

the extent to which antimalarial treatment can be expected to reverse the pathologic process of cerebral malaria. Our finding of similar fatality rates in the artemether and quinine groups suggests that the speed of parasite clearance may be a relatively unimportant determinant of survival. In this case, part of the explanation may be that artemether preferentially accelerates the clearance of younger parasites, which are those seen in the circulation, over more mature parasites, which are located deep in the vasculature and mediate organ damage.<sup>17</sup>

Our study shows that artemether is a well-tolerated and effective alternative to quinine and highlights the potential importance of the artemisinin derivatives in the event that quinine resistance becomes common throughout the world. Whether artemether should now be introduced as a first-line treatment for cerebral malaria in Africa is a strategic question of considerable importance. The World Health Organization currently recommends that artemether not be used as a first-line treatment in Africa, in order to delay the development of resistance to this valuable class of antimalarial compounds.<sup>18</sup> Once the results of clinical trials in other parts of Africa are known, this issue will need to be comprehensively reassessed.

Supported by the special program of the United Nations Development Program, the World Bank, and the World Health Organization for research and training in tropical diseases; and grants from the Netherlands Foundation for the Advancement of Tropical Research (to Dr. Boele van Hensbroek), the Ter Meulen foundation (to Dr. Boele van Hensbroek), and the Medical Research Council (to Drs. Bennett and Kwiatkowski).

*We are indebted to the nursing and medical staff of Royal Victoria Hospital and Sibanor Health Centre, particularly the nurses from the Paediatric Special Care Unit, Dr. H. Memming, Dr. G. Dolan, Dr. C. Richards, Dr. T. McKay, Dr. V. McKay, Dr. W. McGuire, Sr. R. Wilson, L. Bayo, and L. Manneh, for recruitment and follow-up of the study patients; to Dr. T. Peto for helpful discussion; to Dr. P. Reeve and Dr. D. Davidson from the Product Development Unit of the World Health Organization for logistic support; and to Dr. H. Whittle, Prof. M. Levin, Prof. G. Duff, and Dr. L. Carpenter, who acted as trial monitors.*

## REFERENCES

1. Marsh K, Forster D, Waruiru C, et al. Indicators of life-threatening malaria in African children. *N Engl J Med* 1995;332:1399-404.
2. Kwiatkowski D, Molyneux ME, Stephens S, et al. Anti-TNF therapy inhibits fever in cerebral malaria. *Q J Med* 1993;86:91-8.
3. Warrell DA, Molyneux ME, Beales PF. Severe and complicated malaria. *Trans R Soc Trop Med Hyg* 1990;84:Suppl 2:1-65.
4. Waller D, Krishna S, Craddock C, et al. The pharmacokinetic properties of intramuscular quinine in Gambian children with severe falciparum malaria. *Trans R Soc Trop Med Hyg* 1990;84:488-91.
5. Pukrittayakamee S, Supanaranond W, Looareesuwan S, Vanijanonta S, White NJ. Quinine in severe falciparum malaria: evidence of declining efficacy in Thailand. *Trans R Soc Trop Med Hyg* 1994;88:324-7.
6. Hien TT, White NJ, Qinghaosu. *Lancet* 1993;341:603-8.
7. Taylor TE, Wills BA, Kazembe P, et al. Rapid coma resolution with artemether in Malawian children with cerebral malaria. *Lancet* 1993;341:661-2.
8. Molyneux ME, Taylor TE, Wirima JJ, Borgstein A. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. *Q J Med* 1989;71:441-59.
9. Peto R. Clinical trial methodology. *Biomedicine* 1978;28(Special Issue):24-36.
10. ISIS-4 Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995;345:669-85.
11. Brewer TG, Peggins JO, Grate SJ, et al. Neurotoxicity in animals due to arteether and artemether. *Trans R Soc Trop Med Hyg* 1994;88:Suppl 1: S33-S36.
12. White NJ, Warrell DA, Chanthavanich P, et al. Severe hypoglycemia and hyperinsulinemia in falciparum malaria. *N Engl J Med* 1983;309:61-6.
13. White NJ, Miller KD, Marsh K, et al. Hypoglycaemia in African children with severe malaria. *Lancet* 1987;1:708-11.
14. Taylor TE, Molyneux ME, Wirima JJ, Fletcher A, Morris K. Blood glucose levels in Malawian children before and during the administration of intravenous quinine for severe falciparum malaria. *N Engl J Med* 1988;319:1040-7.
15. Salako LA, Walker O, Sowunmi A. Parenteral therapy of moderately severe malaria: comparison of intramuscular artemether and intramuscular sulfadoxine-pyrimethamine. *Trans R Soc Trop Med Hyg* 1994;88:89-91.
16. Nosten F, ter Kuile F, Thwai KL, Maclankirri L, White NJ. Spiramycin does not potentiate quinine treatment of falciparum malaria in pregnancy. *Trans R Soc Trop Med Hyg* 1993;87:305-6.
17. White NJ. Clinical pharmacokinetics and pharmacodynamics of artemisinin and derivatives. *Trans R Soc Trop Med Hyg* 1994;88:Suppl 1:S41-S43.
18. The role of artemisinin and its derivatives in the current treatment of malaria (1994-1995): report of an informal consultation convened by WHO in Geneva 27-29 September 1993. Geneva: World Health Organization, 1994:21-3. (WHO/MAL/94.1067.)