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A CONTROLLED TRIAL OF ARTEMETHER OR QUININE IN VIETNAMESE ADULTS WITH SEVERE FALCIPARUM MALARIA

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ABSTRACT

Background   Artemisinin (qinghaosu) and its derivatives are rapidly effective antimalarial drugs derived from a Chinese plant. Preliminary studies suggest that these drugs may be more effective than quinine in the treatment of severe malaria. We studied artemether in Vietnam, where *Plasmodium falciparum* has reduced sensitivity to quinine.

Methods   We conducted a randomized, double-blind trial in 560 adults with severe falciparum malaria. Two hundred seventy-six received intramuscular quinine dihydrochloride (20 mg per kilogram of body weight followed by 10 mg per kilogram every eight hours), and 284 received intramuscular artemether (4 mg per kilogram followed by 2 mg per kilogram every eight hours). Both drugs were given for a minimum of 72 hours.

Results   There were 36 deaths in the artemether group (13 percent) and 47 in the quinine group (17 percent; P=0.16; relative risk of death in the patients given artemether, 0.74; 95 percent confidence interval, 0.5 to 1.11). The parasites were cleared more quickly from the blood in the artemether group (mean, 72 vs. 90 hours; P<0.001); however, in this group fever resolved more slowly (127 vs. 90 hours, P<0.001), the time to recovery from coma was longer (66 vs. 48 hours, P=0.003), and the hospitalization was longer (288 vs. 240 hours, P=0.005). Quinine treatment was associated with a higher risk of hypoglycemia (relative risk, 2.7; 95 percent confidence interval, 1.7 to 4.4; P<0.001), but there were no other serious side effects in either group.

Conclusions   Artemether is a satisfactory alternative to quinine for the treatment of severe malaria in adults. (N Engl J Med 1996;335:76-83.)

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S INCE the cinchona alkaloids were introduced as a specific treatment for agues 350 years ago, the treatment of severe malaria has changed little. Quinine and quinidine remain the drugs of choice for severe chloroquine-resistant malaria due to *Plasmodium falciparum,* and with the spread of these resistant parasites, the usage of these drugs is increasing.[1] In 1972 scientists in China discovered the antimalarial properties of a group of sesquiterpene lactone peroxides derived from the qinghao plant (*Artemisia annua*).[2] The principal component, qinghaosu (artemisinin), and two derivatives — the water-soluble hemisuccinate artesunate and the oil-soluble artemether — are the most rapidly acting and potent of all antimalarial drugs.[2-8] These compounds retain activity against all malarial parasites, including multidrug-resistant strains of *P. falciparum.* Over 2 million people have received antimalarial treatment with artemisinin, artesunate, or artemether.[4] These drugs have proved rapidly effective in the treatment of severe malaria and remarkably nontoxic.[5-11] Artemether has been reported to reduce the mortality rate for cerebral malaria caused by chloroquine-resistant *P. falciparum* by a factor of 3.[12]

METHODS

This study was conducted in a special research ward at the Center for Tropical Diseases in Ho Chi Minh City, Vietnam, and was approved by the center's ethics and scientific-review committee. A full-time study team of specially trained physicians and nurses provided medical care. All laboratory measurements made during the acute phase of illness were conducted on site. A three-month pilot study was conducted before the main study to familiarize staff members with the clinical and laboratory procedures.

Objectives

The study was designed to detect a difference in mortality of 33 percent with 95 percent confidence and 80 percent power. The mortality rate for severe malaria was approximately 30 percent before the study. Except where indicated the secondary end points were defined prospectively.

Drugs

Patients were randomly assigned to receive artemether (50 mg per milliliter) or quinine dihydrochloride (250 mg per milliliter) for a minimum of 72 hours. The drugs were issued in packs of 10 identical 3-ml ampules by the Kunming Pharmaceutical Company (Kunming, People's Republic of China). Randomly selected ampules were checked for sterility and potency. The initial dose of both drugs was 0.08 ml per kilogram of body weight (4 mg of artemether per kilogram and 20 mg of quinine salt per kilogram), half of which was injected into the anterior thigh of each leg. The maintenance dose was 0.04 ml per kilogram for each drug (2 mg of artemether per kilogram and 10 mg of quinine salt per kilogram) and was given every eight hours.

When the patient could take oral medication reliably, a second independent randomization was performed. Patients received either a single oral dose of 15 mg of mefloquine per kilogram

(Lariam, Hoffmann–LaRoche, Basel, Switzerland) or oral quinine sulfate (Government Pharmaceutical Organization of Thailand, Bangkok) at a dose of 10 mg per kilogram three times daily for up to four days (i.e., for a total of seven days of antimalarial treatment). Treatment with quinine was followed by two tablets of pyrimethamine–sulfadoxine (Fansidar, Hoffmann–LaRoche).

Randomization and Blinding

The drugs for each patient were placed in a coded sealed envelope, and the envelopes were randomized in blocks of 20. Once a patient was enrolled in the study the envelope was opened. Subsequent analysis of efficacy was on an intention-to-treat basis. Although the ampules, drug volumes, and administration schedules of artemether and quinine were identical, the viscosity and color of the two drugs were slightly different. To maintain blinding, a separate team of nurses, who were not otherwise involved with the care of the study patients, drew up and gave the injections. The drugs were kept in an opaque packet in a locked cabinet during the study.

Clinical Procedures

Patients were included in the study if they (or an accompanying relative) gave informed consent, had asexual forms of *P. falciparum* on a peripheral-blood smear, were older than 14 years, were not in the first trimester of pregnancy, were not intravenous drug users, had received less than 3 g of quinine or two doses of artemisinin or a derivative in the previous 48 hours, and had one or more of the following: a score on the Glasgow Coma Scale of less than 11 (indicating cerebral malaria); anemia (hematocrit, <20 percent), with a parasite count exceeding 100,000 per cubic millimeter on a peripheral-blood smear; jaundice (serum bilirubin, >2.5 mg per deciliter [50 μmol per liter]), with a parasite count of more than 100,000 per cubic millimeter on a peripheral-blood smear; renal impairment (urine output, <400 ml per 24 hours; and serum creatinine, >3 mg per deciliter [250 μmol per liter]); hypoglycemia (blood glucose, <40 mg per deciliter [2.2 mmol per liter]); hyperparasitemia (>10 percent parasitemia); and systolic blood pressure below 80 mm Hg with cool extremities (indicating shock).

Each patient underwent a full clinical examination that included a detailed neurologic assessment. A complete blood count, count and estimation of the life-cycle stage of the parasites, biochemical analyses, measurements of plasma glucose and lactate, and blood cultures were done, and plasma was stored for measurement of cytokines, plasma quinine, and coagulation indexes. Arterial-blood gases and pH were measured on admission beginning in April 1992 (when 234 patients had been enrolled). Blood was obtained by a finger-prick for hematocrit measurements and blood smears every 4 hours for the first 24 hours and every 6 hours until three consecutive smears were negative for asexual stages of *P. falciparum*. The degree of parasitemia was determined on the basis of the number of parasitized red cells per 1000 red cells (thin film) or the number of parasites per 400 leukocytes (thick film).

Management and Clinical Monitoring

Patients were cared for according to standard recommendations.[1] All patients were given isotonic saline to restore fluid bal-

TABLE 1. CHARACTERISTICS OF THE PATIENTS ON ADMISSION, ACCORDING TO TREATMENT GROUP.

CHARACTERISTIC*	ARTEMETHER (N=284)	QUININE (N=276)	P VALUE	CHARACTERISTIC*	ARTEMETHER (N=284)	QUININE (N=276)	P VALUE
Age — yr			0.99	Shock — no. of patients (%)	18 (6)	25 (9)	0.27
Median	30	30		Hypoglycemia — no. of patients (%)	23 (8)	18 (7)	0.52
Range	15–79	15–78		Hematocrit — %			0.18
Interquartile range	22–40	22–41		Median	30	31	
Sex — M/F	212/72	213/63	0.49	Range	10–60	6–53	
Previous treatment with quinine for current episode of malaria — no. of patients (%)	155 (55)	149 (54)	0.93	Interquartile range	24–35	25–37	
				Parasite count — ×10⁻³/mm³			0.71
Previous treatment with artemisinin or derivative for current episode of malaria — no. of patients (%)	30 (11)	22 (8)	0.46	Median	90.4	86.9	
				Range	0.02–1680	0.04–3690	
Convulsions — no. of patients (%)	30 (11)	33 (12)	0.59	Interquartile range	16.8–339	19.3–343	
Temperature — °C			0.3	White-cell count — ×10⁻³/mm³			0.06
Median	38.2	38.5		Median	8.35	9.08	
Range	36.3–41	36.5–41		Range	1.9–35	3.5–38.5	
Interquartile range	37.5–39	37.5–39.2		Interquartile range	6.2–11.9	6.5–12.6	
Pulse rate/min			0.87	Serum creatinine — mg/dl			0.25
Median	102	105		Median	2.0	2.0	
Range	70–160	60–188		Range	0.3–11.8	0.5–13.8	
Interquartile range	96–120	95–120		Interquartile range	1.5–3.7	1.4–3.2	
Respiratory rate/min			0.59	Total bilirubin — mg/dl			0.71
Median	28	28		Median	3.6	3.3	
Range	16–64	16–48		Range	0.5–20	0.5–19	
Interquartile range	24–32	24–32		Interquartile range	1.8–7.9	1.6–8.6	
Glasgow Coma score			0.14	Aspartate aminotransferase — μmol/hr/dl			0.78
Median	10	10					
Range	3–15	3–15		Median	153	160	
Interquartile range	8–15	8–15		Range	20–630	30–830	
Glasgow Coma score <11 — no. of patients (%)	142 (50)	148 (54)	0.4	Interquartile range	95–248	100–235	
				Plasma lactate — mmol/liter			0.94
Opening pressure of cerebrospinal fluid — mm of water			0.45	Median	3.2	3.4	
				Range	0.4–19.3	0.4–18.3	
Median	160	165		Interquartile range	2–5.5	2.1–4.7	
Range	50–340	40–510					
Interquartile range	125–190	130–200					

*To convert values for creatinine to micromoles per liter, multiply by 88.4; to convert values for total bilirubin to micromoles per liter, multiply by 17.1.

ance, and fluid balance was maintained with saline or 5 percent dextrose in water. When necessary, a central venous catheter was inserted and the central venous pressure maintained at 5 cm of water. Blood was transfused if the hematocrit fell below 20 percent. Hypoglycemia was corrected with a bolus injection of 50 ml of 30 percent dextrose in water and a subsequent maintenance infusion of 5 to 10 percent dextrose in water. Detailed clinical and nursing observations were recorded a minimum of every 4 hours for the first 24 hours and every 6 hours thereafter.

In all patients blood glucose, lactate, and cytokine levels were measured 4, 8, 12, and 24 hours after admission. Beginning in June 1992 (after the enrollment of 259 patients) an electrocardiogram with a rhythm strip (paper speed, 50 mm per second) was obtained before treatment, 12 hours after treatment was begun, 4 hours after the last parenteral dose of antimalarial agent, and at discharge. Standard intervals were recorded, and the QT interval was corrected with the use of Bazett's formula ($QT/\sqrt{RR}$). A diagnostic lumbar puncture was performed if the score on the Glasgow Coma Scale was below 14. Opening cerebrospinal fluid pressures were measured, the cerebrospinal fluid was analyzed microscopically, and levels of protein, glucose, and lactate were determined. Peritoneal dialysis was started in patients with established renal failure. Beginning in September 1993 (after the enrollment of 427 patients) hemofiltration was also available. There were no facilities for ventilation. Acetaminophen was given for a temperature above 39°C, and intravenous diazepam, intramuscular phenobarbital, and if necessary, intravenous phenytoin were given for convulsions. Antibiotics with no clinical antimalarial activity (i.e., not tetracyclines, macrolides, trimethoprim–sulfamethoxazole, or chloramphenicol) were prescribed for suspected cases of bacterial sepsis.

On discharge a detailed neurologic examination, electrocardiography, and beginning in November 1993 (after the enrollment of 441 patients), audiography (frequency range, 250 to 8000 Hz) were performed. A full autopsy was performed on patients who died of malaria if permission could be obtained from relatives. All information was recorded in the patients' records and then triple-entered in a computer data base.

Statistical Analysis

The study was reviewed continuously by an outside monitor. Categorical data were analyzed by Fisher's exact test, and continuous data by the Kruskal–Wallis test with the statistical programs Statview v.4.1 (Abacus Concepts, Berkeley, Calif.) and Stata v.4 (Stata, College Station, Tex.). The lengths of time to recovery were compared in the two groups by survival analysis with the Peto and Peto modification of the Wilcoxon test.[13] Cox regression analysis was used to determine the contribution of different variables to recovery.

RESULTS

Between May 1991 and January 1996, 561 patients were enrolled in the study. Only one patient was excluded from the analysis, because a review of the admission blood smear did not confirm the presence of malarial parasites. He died of an intracranial hemorrhage. There was a steady decline in the number of patients recruited during the study that paralleled the overall decline in the incidence of malaria in Vietnam. After reviewing the results of an interim analysis conducted in October 1994 (after 500 patients had been recruited), we decided to continue the study for one more year.

The characteristics of the patients on admission are shown in Table 1. There were no significant differences in any of the major variables between the two treatment groups. The median total dose of an-

TABLE 2. ASSESSMENT OF OUTCOME AFTER TREATMENT WITH ARTEMETHER OR QUININE.

VARIABLE	ARTEMETHER (N=284)	QUININE (N=276)	RELATIVE RISK (95% CI)*	P VALUE
	no. of patients/total (%)			
Mortality rate				
Overall	36 (13)	47 (17)	0.74 (0.5–1.11)	0.16
Patients previously treated with quinine or an artemisinin derivative†	18/187 (10)	30/178 (17)		0.045
Patients with no previous treatment†	18/97 (19)	17/98 (17)		0.85
Convulsions	36 (13)	27 (10)	1.3 (0.8–2.1)	0.29
Need for blood transfusion	70 (25)	70 (25)	0.97 (0.73–1.3)	0.85
Need for dialysis	34 (12)	42 (15)	0.8 (0.5–1.2)	0.27
Hypoglycemia	31 (11)	69 (25)	0.44 (0.30–0.64)	<0.001
Decrease in Glasgow Coma score after admission	124 (44)	107 (39)	1.1 (0.9–1.4)	0.27
Gastrointestinal bleeding	34 (12)	42 (15)	0.8 (0.5–1.2)	0.27
Chest infection	64 (23)	56 (20)	1.1 (0.8–1.5)	0.54
Culture-positive urinary tract infection	30 (11)	18 (7)	1.6 (0.9–2.8)	0.1
Culture-negative pyuria	20 (7)	8 (3)	2.4 (1.1–5.4)	0.03
Thigh abscess	1 (0.4)	5 (2)	0.18 (0.02–1.5)	0.1
Leg discomfort causing difficulty walking	5 (2)	7 (3)	0.45 (0.14–1.5)	0.56
No parasite clearance within 7 days	5 (2)	6 (2)	0.81 (0.25–2.6)	0.77

*The relative risk is for the artemether group. The groups were compared by Fisher's exact test for proportions. CI denotes confidence interval.

†This comparison was not specified in the protocol's original analytic plan.

TABLE 3. MULTIVARIATE LOGISTIC-REGRESSION ANALYSIS OF THE FACTORS ASSOCIATED WITH DEATH FROM SEVERE FALCIPARUM MALARIA.

VARIABLE	ADJUSTED ODDS RATIO (95% CI)*	P VALUE
Quinine treatment	1.85 (1.07–3.19)	0.028
Year of study (1993–1996 vs. 1991–1992)	1.47 (0.82–2.66)	0.193
Cerebral malaria†	1.56 (0.89–2.8)	0.12
Shock on admission	4.5 (2.03–9.9)	<0.001
Jaundice on admission	1.66 (0.90–3.1)	0.11
Elevated plasma lactate concentration on admission	2.64 (1.72–4.1)	<0.001
Elevated plasma creatinine concentration on admission	4.0 (2.45–6.6)	<0.001
Elevated hematocrit on admission	1.0 (0.33–1.65)	0.24

*In each case, the odds ratio was adjusted for the other variables listed. CI denotes confidence interval.

†Cerebral malaria was defined as a score of less than 11 on the Glasgow Coma Scale.

timalarial agent given parenterally, including that given before the study, was 120 mg of quinine per kilogram (range, 20 to 246) and 20 mg of artemether per kilogram (range, 4 to 44).

Outcome

The overall mortality rate was 15 percent (83 of 560 patients). The difference in the mortality rate between the artemether group and the quinine group was not significant (13 percent vs. 17 percent, P=0.16) (Table 2). Four patients had neurologic sequelae (three in the artemether group and one in the quinine group), and thus there was also no significant difference in the combined number of deaths and cases of neurologic sequelae between the groups. In a multiple logistic-regression model that incorporated factors identified at the outset as associated with outcome, treatment with artemether was associated with a lower mortality (P=0.028) (Table 3). Among patients with cerebral malaria (score on the Glasgow Coma Scale, <11), the overall mortality rate was 16 percent (45 of 290 patients): 15 percent
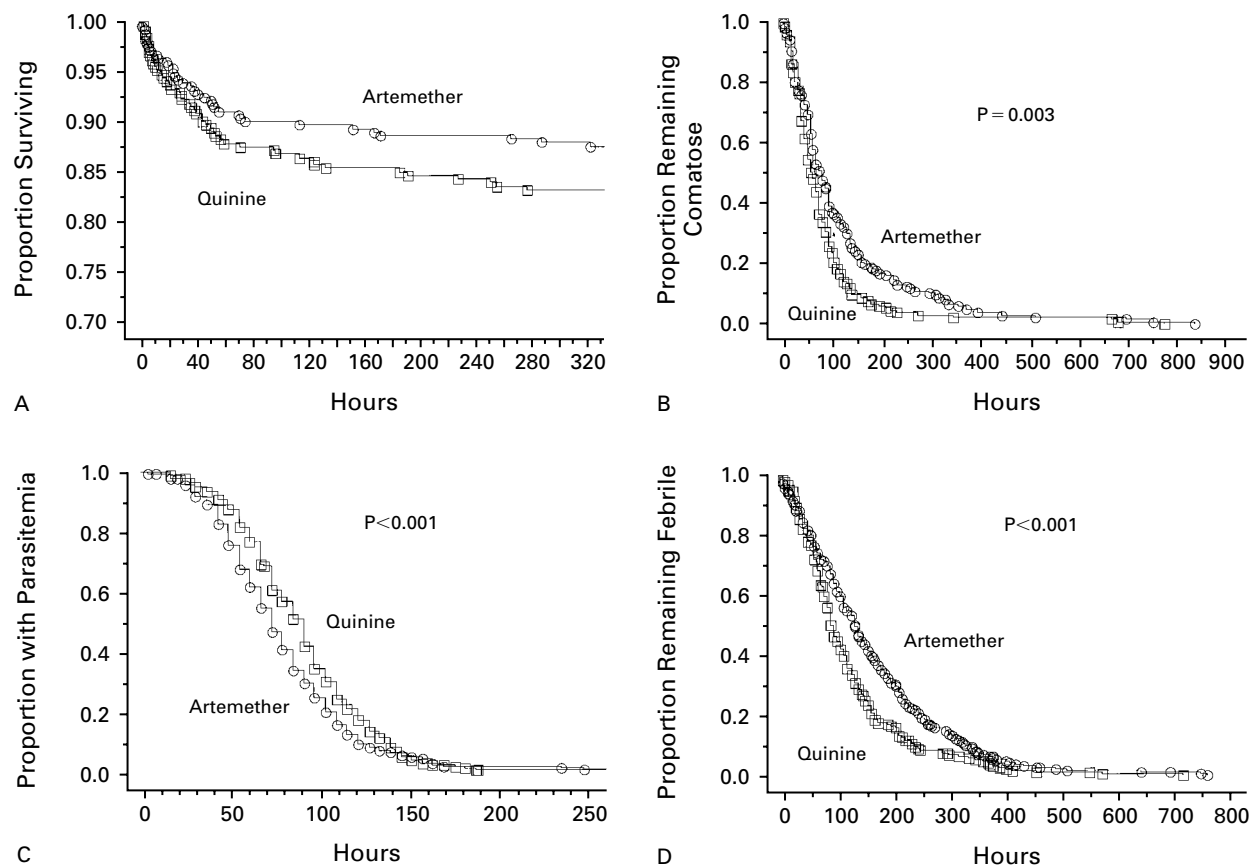

Figure 1. Kaplan–Meier Plots of Overall Survival (Panel A), Time to Recovery from Coma in Patients with Cerebral Malaria (Panel B), Time to Clearance of Parasites from the Peripheral Blood (Panel C), and Time to Resolution of Fever (Panel D).

In Panel C the four patients in whom clearance of parasites took longer than 250 hours (two in the artemether group and two in the quinine group) are not shown.

TABLE 4. ASSESSMENT OF RECOVERY AFTER TREATMENT WITH ARTEMETHER OR QUININE.

VARIABLE	ARTEMETHER (N=284)	QUININE (N=276)	P VALUE*
	hours		
Duration of parenteral antimalarial treatment			0.21
Median	82	80	
Range	56–180	40–168	
Interquartile range	64–108	64–96	
Time for plasma lactate level to fall below 2.5 mmol/liter†			0.97
Median	48	48	
Range	4–168	4–168	
Interquartile range	12–72	12–72	
Time to parasite clearance			
Decrease to 50% of admission value			0.084
Median	10.3	11.5	
Range	2–74	2–189	
Interquartile range	5–16	6–19.5	
Decrease to 10% of admission value			<0.001
Median	19	23.5	
Range	3.5–182	3.5–235	
Interquartile range	13–28	16–34	
Total clearance			<0.001
Median	72	90	
Range	4–330	16–414	
Interquartile range	54–102	66–108	
Resolution of fever			<0.001
Median	127	90	
Range	0–756	0–714	
Interquartile range	60–216	54–144	
Time to Glasgow Coma score of 8‡			0.039
Median	57	42	
Range	4–270	4–258	
Interquartile range	24–90	12–78	
Time to Glasgow Coma score of 11§			0.023
Median	48	30	
Range	4–468	4–480	
Interquartile range	16–84	12–66	
Time to Glasgow Coma score of 15¶			0.003
Median	66	48	
Range	0–828	0–768	
Interquartile range	30–132	20–84	

in the artemether group (21 of 142) and 16 percent in the quinine group (24 of 148, P = 0.75).

Causes of Death

The cause of death was often multifactorial. Of the 83 patients who died, 59 had acute renal failure (dialysis had been started in 30 of these patients), 56 had intractable shock, 35 had a terminal respiratory arrest with continued pulse, 25 had serious gastrointestinal bleeding, and 12 had pulmonary edema. A full autopsy was performed on 50 of the patients who died. Serial measurements of arterial-blood gas were begun in 1992 and showed that 42 of the 50 (84 percent) had metabolic acidosis.

Recovery

Artemether treatment was associated with quicker clearance of parasites from the peripheral blood but slower resolution of fever, slower recovery from coma, and longer hospitalizations (P≤0.005 for all comparisons) (Fig. 1 and Table 4). We used a Cox proportional-hazards model to assess the contribution of different variables evaluated at admission (score on the Glasgow Coma Scale, creatinine and lactate values, log parasite count, and the presence of jaundice, hypoglycemia, and shock) to the time to recovery from coma (defined as the time to reach a score of 15 on the Glasgow Coma Scale). In patients with cerebral malaria, quinine treatment remained significantly associated with a more rapid recovery than artemether treatment (hazard ratio, 1.39; 95 percent confidence interval, 1.06 to 1.81; P=0.017), and this difference became evident after 48 hours (Fig. 1). The markers of disease severity at admission in patients with impaired consciousness that lasted more than 48 hours were similar in the two groups. In a similar model, the differences in the time to resolution of fever between the two groups could not

TABLE 4. CONTINUED.

VARIABLE	ARTEMETHER (N=284)	QUININE (N=276)	P VALUE*
	hours		
Time before patient able to drink			0.35
Median	24	29	
Range	0–760	0–539	
Interquartile range	4–78	8–65	
Time before patient able to eat			0.82
Median	48	45	
Range	0–760	0–592	
Interquartile range	12–95	20–85	
Time before patient able to sit			0.70
Median	82	78	
Range	0–1068	0–1452	
Interquartile range	42–140	48–120	
Time before patient able to stand			0.52
Median	108	96	
Range	0–1200	0–1608	
Interquartile range	60–168	60–144	
Time before patient able to walk			0.38
Median	126	114	
Range	0–1200	0–1608	
Interquartile range	72–200	72–168	
Time before patient able to leave hospital			0.005
Median	288	240	
Range	96–1248	98–1608	
Interquartile range	216–432	192–336	

*The groups were compared by survival analysis with use of the Peto and Peto modification of the Wilcoxon test.[13]

†Only data from patients who survived and whose venous plasma lactate concentrations were above 2.5 mmol per liter on or after admission (171 in the artemether group and 173 in the quinine group) were analyzed.

‡Only data from patients whose scores on the Glasgow Coma Scale were below 8 at any time (110 in the artemether group and 116 in the quinine group) were analyzed.

§Only data from patients whose scores on the Glasgow Coma Scale were below 11 at any time (139 in the artemether group and 140 in the quinine group) were analyzed.

¶Only data from patients whose scores on the Glasgow Coma Scale were below 15 at any time (175 in the artemether group and 174 in the quinine group) were analyzed.

be explained by the occurrence of supervening bacterial infections.

Hematologic Recovery

There was no significant difference between the artemether group and the quinine group in the fall in the hematocrit from base-line values (median reduction, 27 percent vs. 30 percent; range, 0 to 71 vs. 0 to 68; P=0.48), blood-transfusion requirements (Table 2), or the hematocrit values at discharge (22 percent vs. 24 percent; range, 10 to 40 vs. 13 to 41; P=0.18). However, patients in the artemether group had significantly lower mean reticulocyte counts one week after treatment (2.3 percent vs. 5.6 percent; range, 0.1 to 16.1 vs. 0.0 to 28; P<0.001). Blackwater (red or black urine caused by hemoglobinuria but not hematuria) developed in 11 patients: 7 in the artemether group and 4 in the quinine group (2 percent vs. 1 percent; relative risk, 2.7; 95 percent confidence interval, 0.86 to 8.3; P=0.11). The overall incidence of blackwater in patients who had re-

ceived quinine either before or during the trial was 4.9 percent (21 of 431; 95 percent confidence interval, 3.0 to 7.4 percent).

Adverse Effects

Quinine was associated with hypoglycemia: hypoglycemia developed in 25 percent of the quinine-treated patients as compared with 11 percent of the artemether recipients (relative risk, 2.3; 95 percent confidence interval, 1.6 to 3.4; P<0.001). There was an increased incidence of culture-negative pyuria in the artemether group (P=0.03), but the incidence of urinary tract infections was not significantly different between groups. There were no other definite systemic adverse effects. There were no significant electrocardiographic abnormalities in the patients in whom recordings were made, although in 60 of the quinine recipients (45 percent), as compared with 38 of the artemether recipients (25 percent), the corrected QT interval was prolonged by more than 0.5 second (relative risk, 1.8; 95 percent

confidence interval, 1.3 to 2.5; P = 0.001). Only 12 patients in the quinine group (9 percent) and 11 in the artemether group (7 percent) had a corrected QT interval that was prolonged by more than 25 percent (P = 0.67). Prolongation of the corrected QT interval was not associated with any other clinical finding, including the development of shock or the duration of coma. There were no differences between the two treatment groups in auditory acuity on discharge from the hospital.

Oral Treatment

Overall, 247 patients were randomly assigned to receive oral mefloquine and 224 to receive oral quinine; 89 patients did not receive oral antimalarial agents because they had either died (74) or had received seven days of parenteral treatment (15). Nine patients died after receiving oral antimalarial agents (four given mefloquine and five given quinine). The oral antimalarial agents had no effect on recovery times or parasite clearance as assessed by Cox regression analysis.

DISCUSSION

Our results show that artemether is a safe and effective treatment for severe falciparum malaria in Vietnamese adults. The mortality rate among artemether-treated patients was 26 percent lower than that among quinine recipients, but the 95 percent confidence interval ranged from a 50 percent reduction to an 11 percent increase in mortality. However, in our prospectively designed multivariate analysis, which took into account other factors that contribute to outcome, treatment with artemether was associated with a significantly lower mortality rate than treatment with quinine. This suggests that artemether is at least as good as, and may be better than, quinine for severe chloroquine-resistant malaria. In a setting of relative quinine resistance,[14] similar to that in Vietnam,[15] artemether proved considerably superior to quinine in smaller, open trials of severe malaria conducted in Burma and Thailand.[9-11] The large differences in mortality observed in these studies were not substantiated in our large and detailed double-blind, randomized trial. This cannot be ascribed to differences in clinical severity or drug administration, since the clinical and laboratory features of severe malaria in our trial were similar to those reported previously and the doses of artemether were higher than those usually recommended.

Although treatment with artemether resulted in a more rapid reduction in the level of parasitemia (as reported previously[3]), the overall times to defervescence, recovery of consciousness in patients with cerebral malaria, and discharge from the hospital were longer in artemether-treated patients. Survival analysis indicated a significant divergence in the times to recovery from coma among patients who remained unconscious for more than two days. In these patients, treatment with artemether was associated with slower recovery. There are three possible explanations for this unexpected finding: the play of chance, neurotoxicity,[16,17] or a consequence of the beneficial effect of artemether — patients who would have died if they had received quinine survived because they received artemether and took longer to recover. Although there was no other evidence of neurotoxicity, an acute reversible drug effect cannot be excluded, particularly since the difference in the times to recovery from coma became evident after 48 hours, after a total of 14 mg of artemether per kilogram had been given. In support of the third explanation, the times to recovery from coma were strongly associated with other measures of disease severity, and these measures were similar in all patients whose recovery from coma took longer than 48 hours.

In uncomplicated malaria, the artemisinin derivatives consistently shorten all aspects of recovery, whereas in severe malaria, in which the processes that cause organ dysfunction and death may already be largely irreversible,[1] they do not. Pharmacokinetic factors may contribute to this difference. Parenteral artemether is dissolved in groundnut oil and administered by intramuscular injection. As compared with orally administered artemether, intramuscularly administered artemether is absorbed slowly and incompletely. This delay in achieving therapeutic blood levels may offset any intrinsic pharmacodynamic advantage of artemether. In general, the water-soluble artesunate has resulted in the most rapid therapeutic responses.[3] Artesunate is given intravenously and is also rapidly bioavailable after intramuscular or oral administration.[18] Artesunate may be more effective than artemether in severe malaria. By contrast, absorption of intramuscular quinine in severe malaria is regular, and its plasma-concentration profiles are similar to those seen after intravenous administration.[19,20]

The intramuscular administration of quinine is painful and causes local tissue damage, which sometimes results in sterile abscesses[21,22] and, occasionally, tetanus.[23] In this study, both treatment regimens were well tolerated and only nine quinine-treated patients (3.2 percent) had abscess formation, difficulty walking because of local pain, or both, despite the use of a concentrated solution (250 mg per milliliter, with a pH of 2). Thus, the risks of serious local reactions from intramuscular quinine are low, provided a scrupulous aseptic technique of injection is used. Quinine causes hypotension if given too quickly by intravenous injection, and it also prolongs ventricular repolarization, but substantial (>25 percent) prolongation of the corrected QT interval occurred in only 12 patients (9 percent), and no serious toxic effects were associated with the use of a

loading dose of quinine despite the fact that the majority of patients had been treated previously with quinine.[24] Indeed, there were no serious cardiovascular or nervous system effects with either drug.

Quinine is a potent stimulator of the secretion of insulin by pancreatic beta cells[25] and was associated with an increased risk of hypoglycemia. Overall, our results confirm that intramuscular administration of quinine is an acceptable alternative to intravenous administration and that the principal adverse effect of quinine in severe malaria is hypoglycemia.[25] In rodents, dogs, and primates, artemether (and the related compound, arteether) induced an unusual and selective pattern of damage to certain brain-stem nuclei.[16,17] This has been the main concern overlying the further development of these compounds. With the possible exception of prolonged recovery from coma in patients given artemether, we did not detect any evidence of permanent damage to the central nervous system despite the use of maintenance doses that were three times higher than those now usually recommended. The auditory nuclei are among the most sensitive to damage by these compounds, but there was no evidence of residual hearing impairment.

Artemether is an effective alternative to quinine for severe malaria. It is simple to administer, equivalent in overall cost to quinine, and has no apparent local or serious systemic adverse effects. It is one of a family of new antimalarial agents that are active against quinine-resistant parasites. These new drugs should not be used in an uncontrolled or unregulated way, or resistance to them will develop.

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