

Efficacy of Micronized Halofantrine in Semi-Immune Patients with Acute Uncomplicated Falciparum Malaria in Cameroon

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Received 19 January 1993/Returned for modification 15 March 1993/Accepted 21 June 1993

Fifty subjects with acute uncomplicated falciparum malaria were treated orally with a new micronized formulation of halofantrine. The dose given corresponded to one-half the normal dose for the standard formulation. Parasitemia cleared in all subjects within 78 h. There was recrudescence of falciparum malaria in seven subjects after day 14. The mean \pm standard deviation clearance times of parasitemia and fever were 49.0 ± 14.2 and 24.3 ± 13.2 h, respectively. Other clinical symptoms related to malaria cleared within the first 3 days. Pruritus occurred in two subjects, back pain occurred in one subject, and diarrhea occurred in one subject; all of these symptoms were mild. Hematological and biochemical indices were not adversely affected by treatment except in five subjects in whom minor and transitory increases in aspartate aminotransferase and alanine aminotransferase were observed. Micronized halofantrine appears to be a safe, well-tolerated, and effective treatment for acute falciparum malaria in semiimmune patients.

The spread of chloroquine-resistant *Plasmodium falciparum* to most countries in Africa has prompted the development of alternative drugs for the treatment of malaria. Halofantrine has been used since 1988 in France and some West and Central African countries and was demonstrated to be effective in treating resistant falciparum malaria (5, 10, 17). However, a major drawback of halofantrine is its poor and variable absorption and bioavailability between subjects; these have been responsible for a number of treatment failures (3, 11, 12, 15, 18). Therefore, attempts to develop a new micronized formula have recently been made. The goal of the current study was to assess the efficacy and safety of this improved, micronized formulation in an area of intense and continuous malaria transmission in Cameroon.

MATERIALS AND METHODS

Between November 1990 and June 1991, all outpatients with presumptive malaria attending an urban primary health care center in Yaoundé, Cameroon, were subjected to a detailed clinical examination and an examination of thin and thick blood films. Symptomatic patients with parasitemia ranging from 2,000 to 250,000/ μ l who consented to the study were included. Patients with complicated malaria or severe associated diseases, as defined by the criteria of the World Health Organization (21), pregnant women, and children under 10 years of age or weighing less than 26 kg were excluded.

Halofantrine hydrochloride (micronized formulation) was given in the form of 125-mg white uncoated scored tablets provided by SmithKline Beecham (Hertfordshire, United Kingdom). The micronized formulation consists of the halofantrine crystal broken into smaller particles ($\leq 5 \mu$ m) to increase the surface area of the crystal and facilitate solubilization, as demonstrated by increased absorption of doses of up to 300 mg of the drug in volunteers compared with that of the previous formulation. The patients were treated orally with three doses of either 125, 187.5, or 250 mg at 6-h intervals for body weights of 26 to 31, 32 to 40, or 40 kg or

greater, respectively. These doses correspond to one-half the normal dose for the standard formulation of halofantrine (25 mg/kg of body weight). The drug was administered to patients without a specific food regimen. Patients were followed at home, and the intake of the doses was supervised. Investigations including clinical examination, temperature, symptom recording, and blood smears were performed twice daily for the first 4 days and on days 7, 14, 21, and 28 posttreatment. Parasite counts on blood smears were determined twice daily until two successive thick blood smears were negative.

Routine blood examinations (hematocrit, hemoglobin, erythrocyte count, total leukocyte count, and platelet count) were performed before treatment and on days 3, 7, 14, 21, and 28 posttreatment.

Aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase, bilirubin, and creatinine were measured before treatment and on days 3, 7, and 28 posttreatment.

In vitro antimalarial drug susceptibilities (chloroquine, quinine, and halofantrine) were assessed before treatment by an isotopic semimicrotest (13). Briefly, a suspension (700 μ l per well) of parasitized erythrocytes (1.5% hematocrit, 0.2 to 0.5% initial parasitemia) in RPMI 1640 medium supplemented with 10% human serum and buffered with 25 mmol of *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid (HEPES) per liter and 25 mmol of NaHCO₃ per liter was distributed in predosed 24-well plates. The plates were incubated for 42 h at 37°C in 5% O₂-5% CO₂-90% N₂. [³H]hypoxanthine was added 18 h later to assess parasite growth. The contents of each well were collected and washed by using a cell harvester. The amount of radioactivity incorporated by the parasites was measured with a liquid scintillation counter. The 50% inhibitory concentrations (IC₅₀s) were determined by nonlinear regression analysis of log dose-response curves.

Levels in plasma of halofantrine and *N*-desbutyl-halofantrine, the main human metabolite of halofantrine (2), were measured by high-performance liquid chromatography (HPLC) (7) on days 1, 2, and 3 posttreatment. Glucose

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TABLE 1. Summary of clinical data for patients with falciparum malaria treated with micronized halofantrine

Clinical parameter	Value
Total no. of subjects (no. of males/no. of females) ...	50 (35/15)
Age (yr)	
Range	11–54
Mean \pm SD.....	22.2 \pm 8.39
Initial temp ($^{\circ}$ C)	
Range	36.5–40.2
Mean \pm SD.....	38.0 \pm 1.0
Initial parasite density (per μ l)	
Range	2,400–200,000
Geometric mean	16,500
Fever clearance time (h)	
Range	6–67
Mean \pm SD.....	24.3 \pm 13.2
Parasite clearance time (h)	
Range	20–78
Mean \pm SD.....	49.0 \pm 14.2
Day 14 cure rate (%)	100

6-phosphate dehydrogenase (G6PD) was measured before treatment.

No specific antivectional measures were taken by these patients who lived in Yaoundé or in its suburbs, which are areas of high malaria transmission, during the 28-day follow-up period.

RESULTS

Of the 57 patients included in the study, 50 completed the 28-day follow-up. Six patients were lost to follow-up. One subject was excluded because of poor compliance. The clinical and parasitological data for the 50 subjects who completed the follow-up are presented in Table 1. The mean age of these 35 males and 15 females (sex ratio, 2.3) was 22.2 years (range, 11 to 54 years). The median parasitemia level at the time of inclusion into the study was 16,000/ μ l and the geometric mean was 16,500/ μ l (range, 2,400 to 200,000/ μ l).

All 50 patients were free of clinical symptoms on day 3 and had negative blood smears on days 7 and 14 (96% negative smears on day 3). No patient had patent parasitemia at 78 h posttreatment.

The parasite clearance time, defined as the time (in hours) from the start of treatment until two successive blood smears became free of parasites and remained negative for 7 days, was, on average, 49.0 \pm 14.2 h (mean \pm standard deviation; range, 20 to 78 h).

The fever clearance time, defined as the time (in hours) from the start of treatment for the temperature to return to normal (37.5 $^{\circ}$ C) and then remain below 38 $^{\circ}$ C for 12 h, was, on average, 24.3 \pm 13.2 h (mean \pm standard deviation; range, 6 to 67 h).

Recrudescence of falciparum malaria was diagnosed in

seven patients: three patients on day 21 and four patients on day 28.

In vitro susceptibilities to chloroquine, quinine, and halofantrine were assessed against 30 isolates. A total of 14 of 25 isolates were susceptible to chloroquine (mean IC₅₀, 90.9 nmol/liter). All isolates were highly susceptible to halofantrine (n = 24; mean IC₅₀, 4.27 nmol/liter) and quinine (n = 23; mean IC₅₀, 210 nmol/liter) (Table 2).

Two patients spontaneously complained of pruritus, one complained of back pain, and one complained of diarrhea; all of these were mild and resolved rapidly. Clinical examinations were negative for these patients.

Laboratory examinations showed a mild (less than twice the normal value), transitory increase in ALAT or ASAT levels in five patients and an increase in the alkaline phosphatase level in one patient.

The mean \pm standard deviation hemoglobin value before treatment was 12.4 \pm 2.4 g/dl (range, 6.9 to 16.4 g/dl). Following an initial fall to 11.4 and 11.6 g/dl on days 3 and 7, respectively, values increased to 12.1 and 13.4 g/dl on days 14 and 28, respectively. Ten patients had hemoglobin values of less than 10 g/dl pretreatment (lowest hemoglobin value, 6.9 g/dl); the hemoglobin values for these subjects increased after treatment.

Measurement of G6PD levels before treatment showed that it was within the normal limits.

Mean levels of halofantrine and *N*-desbutyl-halofantrine in plasma are reported in Table 3. The mean halofantrine levels in the plasma of treatment failures on days 21 and 28 did not differ (P < 0.05) from those in the plasma of treatment successes.

DISCUSSION

Chloroquine-resistant *P. falciparum* is now commonly encountered in most countries in Africa. Previous studies have shown that halofantrine is an effective drug for the treatment of acute falciparum malaria in areas of chloroquine resistance in Africa (17, 19, 20).

The present study showed that micronized halofantrine given in three divided doses at 6-h intervals is effective in clearing *P. falciparum* in a semi-immune population. All patients had negative blood smears on days 7 and 14. Seven patients had positive blood smears between days 21 and 28, but it is impossible to distinguish reinfection from recrudescence in areas of high malaria transmission. The recrudescences (or reinfection) observed in our patients were probably not due to poor absorption of the drug, since HPLC measurements indicated adequate levels of the drug in plasma. Results are in good agreement with those of pharmacokinetic studies (11, 12, 15, 18). However, the micronized formulation did not improve the large interindividual variability of drug absorption (6). Comparative studies in volunteers and pharmacokinetic studies in patients with

TABLE 2. Results of in vitro susceptibility tests

Drug	IC ₅₀ (nM) ^a		
	Mean \pm SD (range)	Chloroquine-susceptible strains (n = 14)	Chloroquine-resistant strains (n = 11)
Chloroquine	90.9 \pm 61.5 (11.9–242.3)	47.6 \pm 24.8	146.0 \pm 48.1
Quinine	210.5 \pm 103.9 (52.8–460.3)	177.1 \pm 106.3	262.4 \pm 79.6
Halofantrine	4.27 \pm 2.38 (1.74–11.47)	4.9 \pm 2.9	3.6 \pm 1.5

^a Threshold values for resistance were as follows: to chloroquine, >100 nM; to quinine, >450 nM; and to halofantrine, >6 nM.

TABLE 3. Concentrations of halofantrine and *N*-desbutyl-halofantrine in plasma

Day	Concn (ng/ml) ^a	
	Halofantrine	<i>N</i> -Desbutyl-halofantrine
1	429.4 ± 203.6 (77.8–1009.9)	132.9 ± 57.5 (23.1–286.7)
2	143.7 ± 67.8 (57.5–458.0)	130.9 ± 51.9 (20.9–258.3)
3	60.0 ± 25.6 (25.8–158.9)	90.5 ± 34.2 (16.6–169.7)

^a Values are means ± standard deviations (range).

malaria in France have shown no difference in the areas under the curve or the mean plasma concentrations versus time between the standard and micronized forms of halofantrine (7a).

The parasite and fever clearance times were 49.0 ± 14.2 and 24.3 ± 13.2 h, respectively. These values are similar to those obtained with the previous formulation of halofantrine (3, 4, 16), even though only one-half of the dosage of halofantrine (in micronized form) was administered. Clinical symptoms associated with the malaria infection cleared rapidly, and no untoward effect attributable to halofantrine treatment was observed. Only mild pruritus, back pain, diarrhea, and transitory elevations in ALAT, ASAT, and alkaline phosphatase values were detected in the patients.

In previous studies (8, 9, 14) done between 1987 and 1989, 60% of *P. falciparum* isolates in Yaoundé were resistant in vitro to chloroquine. In the present study, 11 (44%) isolates were resistant to chloroquine, and all isolates were highly susceptible to halofantrine (mean IC₅₀, 4.27 nmol/liter), which, at present, is common in West Africa (1).

Our results suggest that micronized halofantrine is a safe and effective antimalarial drug for oral use. Although drug absorption remains highly variable, adequate concentrations of both halofantrine and its metabolite were attained in plasma with one-half of the dose compared with those obtained with the previous formulation of halofantrine. It thus appears to be a satisfactory alternative to the previous formulation of halofantrine for the treatment of acute chloroquine-resistant falciparum malaria in semiimmune patients. Further clinical studies in nonimmune patients and children are needed to determine whether the new formulation of halofantrine offers any benefit over standard formulations.

ACKNOWLEDGMENTS

We are grateful to R. J. Horton for assistance and C. Gillotin and B. Maubert for help in drug dosages and in vitro testing.

This study was supported by grants from SmithKline Beecham.

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