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EFFICACY AND TOLERANCE OF EXTENDED-DOSE HALOFANTRINE FOR DRUG-RESISTANT FALCIPARUM MALARIA IN THAILAND

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Abstract. New treatments for malaria are urgently needed in areas such as Thailand where highly drug-resistant strains of *Plasmodium falciparum* are prevalent. Mefloquine is rapidly losing efficacy and conventional doses of halofantrine are ineffective. We therefore used pharmacokinetic simulation to design an extended-dose halofantrine regimen and tested it in 26 soldiers stationed along the Thai-Cambodian border. Halofantrine was given after meals as three doses of 500 mg each at 4-hr intervals on the first day, followed by 500 mg a day for six days (total dose 4.5 g). Twenty-six soldiers treated with quinine-tetracycline for seven days (Q_7T_7) served as controls. There were no significant differences in efficacy between halofantrine and Q_7T_7 ($P > 0.1$) as assessed by cure rate (92% versus 85%), mean parasite clearance time (82 hr versus 81 hr), or mean fever clearance time (93 hr versus 99 hr). Halofantrine was better tolerated than Q_7T_7. The side effects score was lower (2 versus 11; $P < 0.001$), there were less days on which side effects occurred (2.0 days versus 5.5 days; $P < 0.001$), and fewer patients had adverse effects on every treatment day (4% versus 42%; $P < 0.01$). High-dose halofantrine is as effective and better tolerated than quinine-tetracycline for multidrug-resistant falciparum malaria.

New treatments are urgently needed for drug-resistant falciparum malaria. Mefloquine is but the latest in a series of antimalarials that have rapidly lost efficacy after being introduced for the treatment of malaria in the border regions of Thailand,[1] where drug-resistant *Plasmodium falciparum* parasites are particularly prevalent.[2] Halofantrine is a promising new antimalarial, but cross-resistance with mefloquine is a potential problem[3] and the drug is absorbed erratically.[4] In this study, we attempted to overcome poor absorption by using a repetitive dosage regimen and administering halofantrine with meals, which has been shown to increase its bioavailability.[5]

Even when given with meals, however, the manufacturer's (SmithKline Beecham, Welwyn, Garden City, UK) recommended dose of halofantrine (500 mg taken three times at 6-hr intervals) cured only 50% of *P. falciparum* infections acquired along the Thai-Cambodian border.[6] Drug levels one week after treatment were higher in the patients who were cured, suggesting that a regimen capable of producing sustained, high, blood levels might be successful. We used pharmacokinetic simulation to devise such a regimen and then tested it in soldiers stationed along the Thai-Cambodian border. The efficacy and side effects of halofantrine were compared with those of quinine-tetracycline given for seven days (Q_7T_7), the standard in-hospital treatment for uncomplicated falciparum malaria in this region.[7]

PATIENTS AND METHODS

Patients

Study subjects were recruited from male Thai volunteer soldiers 18 years of age or older who were occupationally exposed to malaria along the Thai-Cambodian border. Patients with cerebral malaria, renal failure, hepatic impairment, shock, hemoglobinuria, or with mixed infections (e.g., *P. falciparum* and *P. vivax*) were excluded. Study volunteers were hospitalized in a nonmalarious area for 21 days and then examined one week after discharge. The reappearance of parasites in the peripheral blood within a month

of treatment was therefore due to late treatment failure rather than reinfection.

Volunteers were randomized by a computer-generated random numbers list to receive seven days of quinine (650 mg orally every 8 hr) with tetracycline (250 mg orally every 6 hr) or oral halofantrine. Each halofantrine dose of 500 mg was given 30 min after a meal containing soy milk, rice, and meat. Halofantrine was given three times at 4-hr intervals on the first day, and 500 mg was then given every morning for six days (total dose 4.5 g). Pharmacokinetic simulation of this regimen was performed using pharmacokinetic software (PCNONLIN; Statistical Consultants, Inc., Lexington, KY) and relied on previously derived pharmacokinetic parameters (Shmuklarsky MJ and others, unpublished data).

Laboratory investigations

Routine hematologic and biochemical tests were performed on admission and after one week in all cases, more often if they were abnormal. Standard thick and thin blood films were examined for *P. falciparum* parasites twice a day until two successive smears were negative (no asexual parasites in 200 microscopic fields), then every other day until discharge and at follow-up. Parasitemia was determined by the number of asexual parasites per 200 white blood cells corrected for the patient's actual leukocyte count.

In vitro drug-sensitivity testing was performed using the radioisotope method described by Webster and others,[2] except that drug dilutions were performed manually rather than by machine. The 50% inhibitory concentration (IC_{50}) was the concentration of antimalarial drug required to inhibit parasite uptake of ^{3}H-hypoxanthine by 50%.

Adverse drug effects

Side effects elicited by checklist were recorded for each treatment day on a standardized code sheet. Symptoms were assessed as mild or severe using predetermined criteria agreed on by the three physicians responsible for gathering side effects data. These criteria were numerical whenever possible. For example, one or two loose stools was considered mild diarrhea, three or more was severe; one or two episodes of vomiting was considered mild, three or more was severe. Attempts were made to be as objective as possible when numerical measures were not applicable. For example, a headache noted by the patient that did not interfere with sleep was considered mild, and a headache requiring repeated symptomatic treatment and prohibiting sleep was severe. Adverse effects code sheets were filled out at approximately the same time every morning and the patient was carefully instructed to report any symptom noted during the previous 24-hr period. Frequent checks were made during the study to ensure that the criteria were reproducible when side effects data were gathered by different physicians.

A side effects score was tabulated for each patient without knowledge of the treatment drug. A score of one was given for every mild symptom and a score of three for every severe symptom. Patients were assigned a score every day derived by adding the number of mild (one point per symptom) and severe (three points per symptom) effects reported for the previous 24-hr period. If no side effects were reported, the score for that day would be zero. The total side effects score was the sum of the seven daily scores, one score for each day of treatment. Symptoms reported by the patient during the day prior to treatment were not included in the tabulation since they could not be attributed with certainty to the effects of medication.

Data analysis

The parasite clearance time (PCT) was the number of hours between the first dose of medication and the first of two successive negative blood films; the fever clearance time (FCT) was the interval between the first dose and the time at which the patient became and remained afebrile (< 37.2°C). The study groups were compared using the Student's *t*-test for normally distributed values and the Mann-Whitney U test for those not normally distributed. Two-tailed tests of significance were calculated in all cases.

RESULTS

Efficacy

There were no significant differences on admission between the 26 patients randomized to receive Q_7T_7 and the 26 who received halofantrine (Table 1). Both regimens were effective

TABLE 1
Comparability of study groups on admission

Characteristic*	Treatment	
	Halofantrine	Quinine-tetracycline
Parasitemia/μl†	24,095 (1,341–97,295)	16,834 (1,012–91,212)
IC_{50} of halofantrine (ng/ml)†	1.6 (0.1–18.8)	0.8 (0.1–5.6)
IC_{50} of quinine (ng/ml)†	159 (56–574)	130 (42–641)
Age (years)‡	25.0 (5.0)	24.2 (4.8)
Weight (kg)‡	57.9 (5.2)	61.1 (7.0)
Leukocytes/μl‡	6,913 (2,171)	6,528 (2,206)

* There were no significant differences ($P > 0.1$) between groups for any admission characteristic.
† Values are the median (range).
‡ Values are the mean (SD).

(Figure 1), but neither was significantly better. Parasites were cleared initially in all 52 patients; the PCT was 82 hr (95% confidence interval [CI] 71–93 hr) for halofantrine and 81 hr (95% CI 72–90 hr) for quinine ($P > 0.1$). Asexual parasites reappeared in two halofantrine-treated patients (on days 21 and 28) and in four patients who had received quinine (on days 17, 19, 24, and 28). Although halofantrine gave a slighter higher cure rate than quinine (92% versus 85%) and a shorter FCT (93 hr versus 99 hr), these differences were not significant ($P > 0.1$).

Halofantrine plasma concentrations were determined at periodic intervals during treatment of 10 cured malaria patients (detailed methods and results to be given in a separate report). The mean ± SD halofantrine maximum concentration (Cmax) was 1,924 ± 927 ng/ml on day one and 2,582 ± 852 ng/ml on day six. The mean ± SD halofantrine concentrations on day eight were 511 ± 404 ng/ml. A limited number of plasma drug concentrations were determined in the two halofantrine treatment failures.

Plasmodium falciparum isolates from 47 patients were tested for in vitro sensitivity to halofantrine. The median IC_{50} was 0.9 ng/ml (range 0.1–18.8 ng/ml); (95% CI 0.6–2.0 ng/ml). Isolates from the two halofantrine treatment failures were resistant to halofantrine in vitro; one isolate had the highest IC_{50} found (18.8 ng/ml) while the IC_{50} of the other (3.2 ng/ml) was above the upper 95% CI.

Adverse effects

Halofantrine was better tolerated than quinine-tetracycline (Figure 2). The median side effects score in the halofantrine-treated group was 2 (range 0–12) compared with 11 (range 0–38) in the quinine-treated group $P < 0.001$). The median number of days on which side effects were reported during therapy was 2 (range 0–7) for halofantrine and 5.5 (range 0–7) for quinine ($P < 0.001$). Only one (4%) halofantrine-treated patient complained of side effects every treatment day compared with 11 patients (42%) receiving quinine-tetracycline ($P < 0.01$, by chi-square test with Yates' correction). Self-limited diarrhea on the first or second treatment day occurred in 16 patients (62%) and was the most common side effect of halofantrine (Table 2). Other common adverse effects were dizziness (19%) and vomiting (19%). In no case were side effects severe enough to require a change in medication.

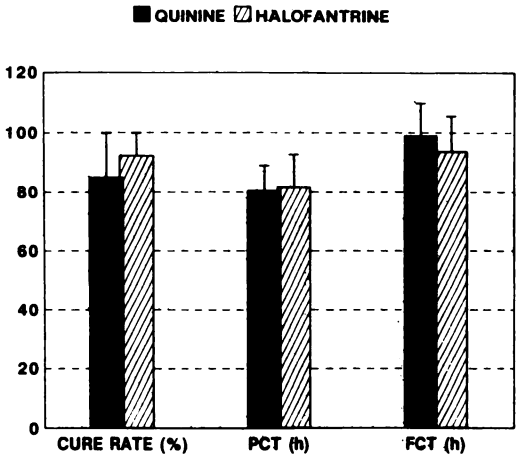

FIGURE 1. Treatment efficacy (mean with upper 95% confidence interval). There were no significant differences in cure rate, parasite clearance time (PCT), or fever clearance time (FCT) between patients treated with halofantrine or quinine-tetracycline ($P > 0.1$). h = hours.

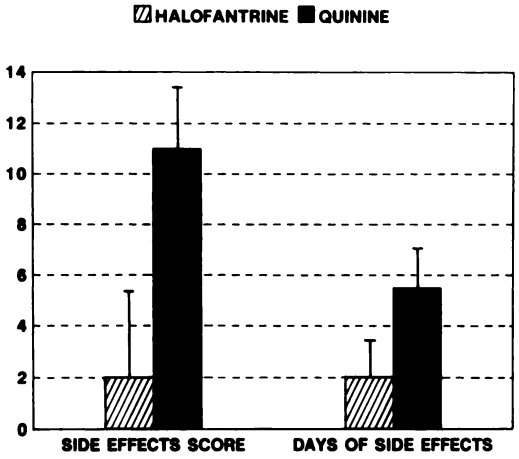

FIGURE 2. Adverse effects (median with upper 95% confidence interval). Treatment with quinine-tetracycline for seven days gave a higher side effects score and side effects occurred on more days than with halofantrine ($P < 0.001$).

TABLE 2
*Number (%) of patients with side effects**

Symptom	Treatment	
	Halofantrine	Quinine-tetracycline
Diarrhea	16 (62)	9 (35)
Hearing difficulty	2 (8)	14 (54)
Tinnitus	1 (4)	13 (50)
Vomiting	5 (19)	8 (31)
Nausea†	4 (15)	7 (27)
Dizziness	5 (19)	2 (8)
Abdominal pain	1 (4)	5 (19)
Headache	2 (8)	1 (4)
Blurred vision	1 (4)	2 (8)
Restlessness	1 (4)	0 (0)

* Includes any treatment emergent symptom reported during the first seven days that was not present in the 24 hr prior to admission.
† All patients with vomiting also had nausea, but nausea was present prior to admission in several cases and was therefore not tabulated as a treatment emergent symptom.

Neither regimen was associated with serious hematologic or biochemical toxicity. Four quinine- and two halofantrine-treated patients ($P > 0.1$) had normal serum transaminase levels on admission and minor, transient elevations of serum alanine aminotransferase (ALT) one week later. The ALT levels subsequently returned to normal in every case.

DISCUSSION

This study demonstrates that halofantrine can be used successfully to treat multidrug-resistant falciparum malaria when given as a loading dose (1,500 mg given over an 8-hr period), followed by a maintenance dose of 500 mg per day for six days. This regimen was designed to rapidly achieve effective plasma drug concentrations and to maintain effective levels throughout the treatment period. Computer simulation based on the known pharmacokinetics of the drug was used to optimize the dosage schedule. This halofantrine regimen was as effective as quinine-tetracycline and better tolerated (Figures 1 and 2). Compared with the usual regimen of 500 mg given at 6-hr intervals without regard to food intake, the halofantrine plasma concentrations are substantially higher using the extended regimen with food. For example, comparing our data with a study of Thai patients with acute uncomplicated falciparum malaria reveals that the mean halofantrine concentrations on day one and day six were approximately two-fold and 12-fold higher, respectively.[8]

We attempted to understand why halofantrine treatment was unsuccessful in two of the 26 patients. Previous investigators have attributed therapeutic failure to poor drug absorption,[4,6,9] but this was not the major factor in our two cases of late recrudescence. One failure was clearly the result of infection with a highly resistant parasite. The IC_{50} for halofantrine in this case was 18.8 ng/ml, the highest value among the 47 isolates tested. Parasites whose IC_{50} exceeds 2.0 ng/ml are considered halofantrine-resistant.[10] There was no evidence of poor drug absorption; this patient's peak halofantrine level on day one (2,495 ng/ml) surpassed the study mean (1,924 ng/ml). The second patient was also clearly infected with a resistant parasite; the halofantrine IC_{50} (3.2 ng/ml) exceeded the upper 95% CI. The small number of plasma halofantrine concentrations available in this case suggest that suboptimal drug levels could have combined with parasite drug-resistance to produce a poor therapeutic outcome. The halofantrine concentration on day eight (406 ng/ml) was slightly lower than the mean ± SD value of 511 ± 404 ng/ml. Treatment failure could theoretically result from a population of highly resistant parasites being selected by drug pressure. This is an unlikely explanation for our two treatment failures. The halofantrine IC_{50} of recrudescent isolates was lower than for pretreatment isolates in both cases; 16.5 ng/ml compared with 18.8

ng/ml in one patient and 1.4 ng/ml compared with 3.2 ng/ml in the other. One would expect the IC_{50} at recrudescence to be higher if a resistant population of parasites had emerged during treatment.

The results obtained with quinine were encouraging in that despite a steady erosion of the susceptibility of Thai falciparum parasites to the effects of quinine in vitro,[7] the combination of quinine with tetracycline remains clinically effective. A previous study conducted in this part of Thailand showed that parasites and fever were cleared promptly by this combination, but long term cure rates were not measured.[7] Our cure rate of 85% is similar to the rate of 90% reported in another Thai study in which patients were monitored for 28 days after treatment.[11]

The halofantrine regimen we used is more practical than standard therapy, which requires administering quinine three times a day and tetracycline four times a day. The loading dose and initial maintenance doses could be given in the hospital; the remaining maintenance doses could be taken after breakfast at home. We gave halofantrine on a full stomach to optimize its absorption. This study and others[6] demonstrate that patients with uncomplicated malaria can eat, but a regimen that does not mandate that medication be administered on a full stomach would be preferable.

Our study was performed prior to reports of halofantrine-induced electrocardiographic (ECG) changes.[12] We did not perform ECGs, but no clinically evident cardiotoxicity or other toxicity was observed. Prospective studies are currently being performed to define the cardiac effects of different halofantrine regimens, including the one used in this study. Other studies should focus on finding the safest, most practical halofantrine regimen that remains effective. There is an urgent need for these investigations since there are currently few options for treating mefloquine-resistant falciparum malaria.

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