CLINICAL TRIAL OF HALOFANTRINE WITH MODIFIED DOSES FOR TREATMENT OF MALARIA IN THE HOSPITAL FOR TROPICAL DISEASES

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Abstract. The spread of falciparum malaria resistant to chloroquine all over Southeast Asian continent has led to increasing use of alternative antimalarial drugs. Halofantrine has been shown to be effective against multidrug resistant *Plasmodium falciparum*. One hundred and twenty falciparum malaria cases were randomly assigned to one of three different halofantrine regimes. Group I (HA1) received 500 mg three times daily for 3 days (total dose: 4,500 mg), group II (HA2) received 500 mg three times daily for the first and the third day (total dose: 3,000 mg) and group III (HA3) received 500 mg three times for one day followed by 500 mg once daily for 7 days (total dose: 4,500 mg). No significant difference in the cure rate was observed among the three regimes (cure rate: 89%, 73%, 97% respectively). However, the cure rate was significantly higher in the HA3 group when compared to the HA2 group. There were no overt cardiac problems seen in this study. Thus, halofantrine has high efficacy in the recommended treatment dose of 500 mg three times after meals on the first day followed by 500 mg once a day after a meal for 7 days (total dose: 4,500 mg).

INTRODUCTION

Following the appearance of chloroquine resistance in *Plasmodium falciparum* in 1957 (Harinasuta *et al*, 1962) and its rapid dissemination throughout Thailand, treatment failures have led physicians to modify antimalarial drug dose regimens (Looareesuwan *et al*, 1992a,b,c; Reacher *et al*, 1981; Chongsuphajaisiddhi *et al*, 1983). The cure rate of mefloquine 15 mg/kg as a single dose (the current first-line drug for patients with slides positive for falciparum malaria in Thailand) was 71% in 1990 (Nosten *et al*, 1991) and the cure rate of quinine plus tetracycline for 7 days (the standard treatment for symptomatic falciparum malaria) was only 90% (Looareesuwan *et al*, 1992d). Halofantrine (a phenanthrene methanol), which has been licensed for the treatment of falciparum malaria in the United States, was originally tested in Thailand in the early 1980s, and found to give high cure rates (over 90%) (Boudreau *et al*, 1988). However, efficacy has gradually decreased over the subsequent years, possibly due to increased parasite cross-resistance or to the low doses given (Bunnag *et al*, 1993). Clinical studies in the Thai-Myanmar and Thai-Cambodian borders confirmed the decreased efficacy of halofantrine in areas with high grade mefloquine resistance (ter Kuile *et al*, 1993; Boudreau *et al*, 1988). Cure rates improved when doses higher than those normally recommended were used (ter Kuile *et*

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al, 1993). Since then it has become clear that halofantrine prolongs ventricular repolarization (prolongation of the QT interval) and is therefore potentially cardiotoxic (ter Kuile *et al*, 1993; Nosten *et al*, 1993; Castot *et al*, 1993; Monlun *et al*, 1993). We therefore evaluated the efficacy and toxicity of halofantrine in different doses for acute uncomplicated falciparum malaria treatment in 1990.

MATERIALS AND METHODS

Patients admitted to the Bangkok Hospital for Tropical Diseases, Thailand, between October 1992 and February 1993, were accepted into the study if they were diagnosed as having acute, uncomplicated falciparum malaria with parasite counts more than 1,000 per μl, if they were between 16-60 years old, weighed more than 40 kg, gave informed consent to take part in the clinical investigation, and agreed to remain in hospital for at least 28 days. Reasons for exclusion were pregnancy, severe malaria [defined by WHO criteria 1990 (Warrell *et al*, 1990)], and history of antimalarial drug treatment within the preceding week. This study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University.

All patients were admitted to the hospital and remained there for 28 days (to exclude reinfection). Body temperature, pulse, and respiratory rates were recorded every 4 hours and blood pressure was measured every 12 hours throughout the study. Clinical signs and symptoms were evaluated every day for the first 7 days and weekly thereafter. Side effects were defined as signs and symptoms that first occurred or became more severe after treatment started. Cure was defined as no recrudescence during 28 days' follow-up (WHO, 1984).

Prior to treatment, we performed a complete blood count including white cell differential and platelets, and hemoglobin level, electrolytes, total and direct bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, albumin, globulin, and aspartate and alanine aminotransferases. These tests were repeated weekly for 4 weeks. Urine was tested for sulphonamides and 4-aminoquinolines before treatment was started. The results of these tests helped us to confirm recent antimalarial treatment history. Only residual concentrations of the drugs were found; the proportions of the treatment groups with positive urine tests were similar. Stool specimens were examined for ova and parasites. Thick and thin blood films were prepared from finger-prick blood samples and stained with Field's stain. Blood smears were obtained every 6 hours after the initial treatment until they were negative and once daily thereafter. We counted either the number of asexual parasites per 1,000 red blood cells in a thin film or per 200 white blood cells in a thick film. Parasite density was calculated from the red blood cell or white blood cell count and expressed as parasites per μl. Blood films were considered negative if no parasites were seen in 200 oil immersion fields in a thick blood film. Parasite clearance time was the time from the start of treatment until the first time the slide was negative. Fever clearance time was the time from the start of treatment until the oral temperature fell to 37.5ºC and did not rise above 37.5ºC again.

The patients were randomly assigned to one of the following treatment groups. Group I (HA1) received halofantrine 500 mg three times daily after meals for 3 days (total dose: 4,500 mg). Group II (HA2) received halofantrine 500 mg three times daily after meals on the first and the third day (total dose: 3,000 mg). Group III (HA3) received halofantrine 500 mg three times after meal on the first day followed by 500 mg once a day after meals for 7 days (total dose: 4,500 mg).

The 12-lead electrocardiography (ECG) were performed as the following schedule.

HA1: pre-treatment, 8 hr, 16 hr, 24 hr, 32 hr, 40 hr, 48 hr, 56 hr, 64 hr, and day 28
HA2: pre-treatment, 8 hr, 16 hr, 48 hr, 56 hr, 64 hr, and day 28
HA3: pre-treatment, 8 hr, 16 hr, 24 hr, 48 hr, day 3, day 4, day 5, day 6, and day 28.

The QT intervals were measured. Since the QT intervals may not always accurately reflect the recovery time of ventricles, the corrected QT (QTc) intervals were calculated by using Bazett's formula ($QT/\sqrt{RR}$) (Bazett, 1920).

Normally distributed data for two groups were compared by the Student's *t*-test. Proportional data were examined by the chi-square test.

RESULTS

One hundred and twenty patients were studied. The three groups were comparable before treatment both in clinical and laboratory characteristics (Table 1).

After treatment 5, 12 and 7 patients in the 3 groups respectively dropped out from the study for social reasons unrelated to drug treatment or side effects. A total of 96 patients remained in the hospital for a full 28-day follows up. Only patients who were followed for 28 days were included in the calculations for drug efficacy. No significant differences in the cure rate among the three groups were observed. The cure rates were 89% (31/35) for HA1, 78% (22/28) for HA2, and 97% (32/35) for HA3, respectively (Table 2). There was an approximately 7-fold risk (RR = 7.07, 95%CI = 0.90-55.28, p = 0.03) of developing

Table 1
Clinical and laboratory characteristics of study groups before treatment.

	HA 1 (n = 40)	HA 2 (n = 40)	HA 3 (n = 40)	p-value
Male/Female	37/3	34/6	34/6	0.50
Age (yr)				
Mean (SD)	25.2(8.7)	23.3(6.4)	24.6(6.7)	0.50
Range	16-48	16-39	16-45	
Mean (SD) height in cm	162.1(6.6)	161.2(7.8)	160.2(6.7)	0.48
Mean (SD) weight in kg	52.0(6.6)	50.6(7.2)	50.8(6.9)	0.62
Fever				
Duration before admission (days)	4.6(3.3)	4.8(4.1)	3.9(2.0)	0.43
Highest fever before treatment (ºC)	38.3(0.7)	38.0(0.8)	38.3(0.8)	0.13
No. of patients with:				
Splenomegaly	7	5	3	0.40
Hepatomegaly	5	3	5	0.71
Urine positive for drugs[a]	19	19	20	0.99
First malaria attack	15	13	17	0.65
Geometric mean parasite count (per µl)	12,980	12,493	18,625	>0.05
Range	523,640-3,570	270,080-2,940	332,640-1,260	
Laboratory data [mean (SD)]				
Packed cell volume (%)	34.4(6.4)	34.3(7.3)	36.2(7.0)	0.39
WBC count (per µl)	6,188(2,058)	6,085(2,205)	6,657(1,698)	0.40
Blood urea (mmol/l)	15.1(9.3)	15.1(10.0)	18.4(9.8)	0.22
Serum creatinine (µmol/l)	1.1(0.3)	1.0(0.2)	1.1(0.2)	0.10
Total bilirubin (µmol/l)	1.5(0.8)	1.3(0.6)	1.4(0.7)	0.45
Serum ASAT	56.0(53.0)	37.0(22.0)	51.6(45.8)	0.11
Serum ALAT	52.9(41.3)	33.3(27.4)	45.4(39.2)	0.06
Albumin (mg/l)	3.9(0.4)	3.8(0.4)	3.9(0.3)	0.38
Alkaline phosphatase	32.5(12.2)	31.4(12.4)	34.5(13.1)	0.54

WBC = white blood count; ASAT, ALAT = aspartate and alanine aminotransferases (IU x 10^3/l).
[a]Sulphonamides and 4-aminoquinolones.

recrudescence in HA2 when compared with HA3. Recrudescence in the all groups occurred between 12 and 28 days after treatment. Seventeen patients (17/125 or 13%) stayed in the hospital for an additional (35 days) week. One patient in group HA1 (pt No. 75) was positive for asexual falciparum parasites on day 29 after treatment, but this patient would be classified as a cure according to the WHO guidelines (WHO, 1984). All recrudescent patients were subsequently treated with quinine plus tetracycline for 7 days. Two patients in group HA1 had asexual *P. vivax* parasites in peripheral blood smear on days 23 and 26 after initial treatment. These patients were treated with a single dose of 450 mg base chloroquine and a full course of 15 mg primaquine per day for 14 days after the study to prevent relapse.

Fever and parasite clearance times were not significantly different among the three groups (p = 0.59; p = 0.23, respectively) except for the parasite clearance times of HA2 and HA3 (64.3±18.8 *vs* 77.2±27.1; p = 0.04, respectively). Clinical improvement occurred between 1 and 3 days after starting treatment in all three treated groups.

Signs or symptoms developing after treatment in the group I, II and III treated groups included headache (28, 26, 29%), dizziness (25, 27, 24%), nausea (16, 20, 8%), vomiting (8, 2, 3%), abdominal pain (7, 2, 8%) and diarrhea (10, 3, 8%). Only dizziness was singificantly less in HA2. One patient in group HAI developed itching 2 days after dosing which disappeared on day 5 after symptomatic treatment. These symptoms occurred between the first to fourth days of treatment and coincided with high fever. It was difficult to distinguish whether they were symptoms of acute malaria or side effects of the drugs.

The ECG study revealed prolongation (more than 440 msec) of QTc intervals in all

Table 2
Therapeutic responses.

	HA 1 (n = 40)	HA 2 (n = 40)	HA 3 (n = 40)	p-value
No. of patients with 28 days[a] follow up	35	28	33	0.41
No. (%) cured at 28 days	31 (89%)	22 (73%)	32 (97%)	0.08
Recrudescence on days : (median)	22	27	23	>0.05
(range)	(12-28)	(15-28)		
Fever clearance time (hr)[b]				
Mean (SD)	60.5(41.1)	53.2(38.1)	63.3(37.3)	0.59
Range	4-180	4-134	4-174	
Parasite clearance time (hr)[c]				
Mean (SD)	71.9(36.8)	64.3(18.8)	77.2(27.1)	0.23
Range	23-141	36-107	19-143	
No. of patients with *P. vivax*	2	0	0	0.17
days of appearance	23,26			

[a]Cure rate at 28 day:
HA 1 *vs* HA 2, p = 0.28
HA 1 *vs* HA 3, p = 0.19
HA 2 *vs* HA 3, p = 0.03
[b]FCT : not significant difference between groups
[c]PCT : HA 1 *vs* HA 2, p = 0.31
HA 1 *vs* HA 3, p = 0.50
HA 2 *vs* HA 3, p = 0.04

Table 3
Adverse events.

	HA1 (n=35)	HA2 (n=28)	HA3 (n=33)	p-value
Headache	28	26	29	0.32
Dizziness	25	27	24	0.03
Nausea	16	20	8	0.06
Vomiting	8	2	3	0.13
Abdominal pain	7	2	8	0.20
Diarrhea	10	3	8	0.21

Table 4
QTc intervals (msec).

	HA1 (n=35)	HA2 (n=28)	HA3 (n=33)
Pre-treatment	399±78	403±19	408±21
8 hr	422±31	422±31	417±29
16 hr	443±35	443±39	440±42
24 hr	452±42	-	442±52
32 hr	466±42	-	-
40 hr	465±40	-	-
48 hr	464±44	438±30	438±36
56 hr	473±40	446±37	-
64 hr	463±39	456±34	-
Day3	-	-	439±36
Day 4	-	-	448±36
Day 5	-	-	445±36
Day 6	-	-	442±20
Day 28	392±79	408±21	406±16

Table 5
QTc intervals percentage changes.

	HA1 (n=35)	HA2 (n=28)	HA3 (n=33)
8 hr	106±11	104±19	102±13
16 hr	111±18	110±16	108±23
24 hr	113±16	-	108±16
32 hr	117±20	-	-
40 hr	116±29	-	-
48 hr	116±23	109±14	107±20
56 hr	119±23	111±26	-
64 hr	116±23	113±20	-
Day3	-	-	108±19
Day 4	-	-	110±22
Day 5	-	-	109±23
Day 6	-	-	108±14
Day 28	98±32	101±10	99±12

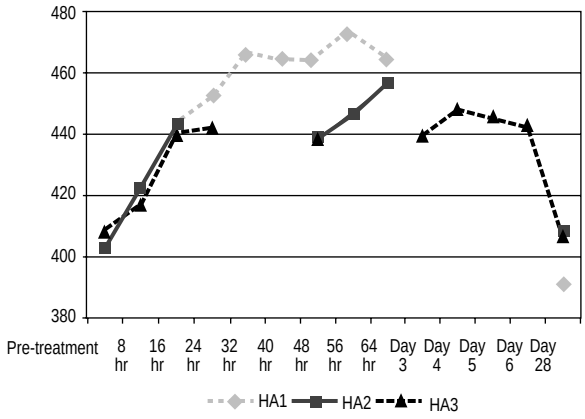

Fig 1–QTc intervals (msec).

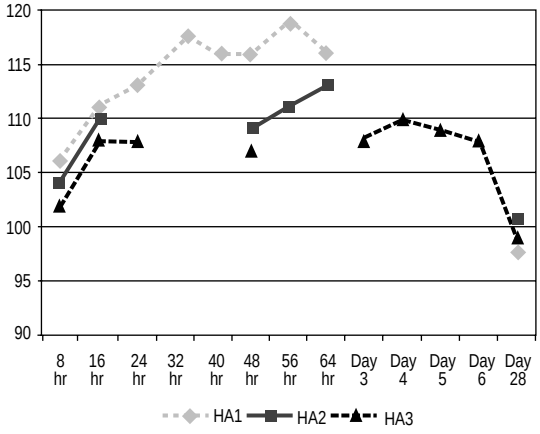

Fig 2–QTc intervals percentage changes.

groups and there was a significant QTc percentage change in HA1 (Tables 4, 5, Figs 1, 2). However, there was no clinically evident cardiotoxicity or serious hematologic or biochemical toxicity or death during the study.

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 one day), followed by a maintenance dose of 500 mg daily for seven days (HA3). Comparison to the lower dose regimen (HA2), this regimen was 7 times more effective (RR = 7.07, 95%CI

= 0.90-55.28, p = 0.03). The efficacy of this regimen was similar to the three days high dose regimen. Several previous studies also showed a very impressive cure rates (Rinehart *et al*, 1976; Cosgriff *et al*, 1982; Boudreau *et al*, 1988; Watkins *et al*, 1988; Chitchang *et al*, 1988). In contrast, the parasite clearance time in HA3 was significantly longer than HA2 (64.3±18.8 *vs* 77.2±27.1 hr, p=0.04) which was probably due to the dosing and frequency of drug administrations.

Since the cardiotoxic effects of halofantrine were first reported in 1993 (ter Kuile *et al*, 1993), many reports have confirmed this potential adverse effect. Overt cardiac problems were not seen in this study. However, Matson *et al*. (1996) demonstrated that the use of standard-dose regimen (24 mg/kg/day) was associated with lengthening of the QTc interval especially when taken with high-fat meal (Shanks *et al*, 1992) but it did not occur in this study. It would be of interest to determine that the seven-day regimen used in this study is associated with less QTc prolongation than the three-day high dose regimen. It is also possible that the failure to show cardiac phenomena is due to a low fat diet which is favored amongst Thai people, and might similarly be expected in other endemic countries where low fat diets are the norm. In addition, no intravascular hemolysis (Vachon *et al*, 1992; Mojon *et al*, 1994) and convulsive encephalopathy (Roblot *et al*, 1990) both potentially serious complications of halofantrine treatment were not observed. However, there was a patient in group HAI who developed pruritus. This has been observed in previous studies, with an estimated frequency of 2-13% (Hallwood *et al*, 1989; Sowunmi *et al*, 1989). It should be emphasized that pruritus is a common accompaniment to antimarial treatment, especially with chloroquine, in Africa, but is less commonly seen in other parts of the world.

In conclusion, halofantrine has high efficacy in the recommended treatment dose of 500 mg three times after meal on the first day followed by 500 mg once a day after meals for 7 days (total dose: 4,500 mg). Further studies should be conducted to determine whether this regimen is safer than the three day high dose regimen required for cure of multi-drug resistant falciparum malaria in Thailand.

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