CLINICAL TRIALS WITH HALOFANTRINE IN ACUTE UNCOMPLICATED FALCIPARUM MALARIA IN THAILAND

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Abstract. The antimalarial efficacy of halofantrine was compared with mefloquine in an open-label, randomized comparative trial in adult male patients with acute uncomplicated falciparum malaria. Twenty-eight patients received halofantrine and 27 received mefloquine. Halofantrine was administered in 3 doses of 500 mg at 6 hour intervals and mefloquine was administered in divided doses of 1,250 mg or 1,500 mg depending on whether the patients weighed less than or more than 60 kg. The patients were followed for 42 days and observed for drug tolerance and evidence of recrudescence.

Response to treatment was favorable with both drugs, but three patients (two treated with halofantrine and one with mefloquine) did not completely eliminate malaria parasites from peripheral blood films in seven days. The parasite and fever clearance times were 75.6 and 55.7 hours, and 80.1 and 61.3 hours, respectively for halofantrine and mefloquine. However, 12 patients recrudesced during the 42 day follow-up period. Nine of these had been treated with halofantrine and three with mefloquine. The 42-day cure rate for the two drugs was 56% and 84%, respectively.

The side-effects of halofantrine and mefloquine were comparable and transient. These are diarrhea, dizziness, orthostatic hypotension and black out. However, vomiting was found to be more common in mefloquine group (41% vs 22%).

INTRODUCTION

The emergence of strains of *Plasmodium falciparum* resistant to chloroquine and other widely used antimalarials and the development of insecticide resistance by mosquitos have created serious problems in the control of malaria. This has necessitated the search of alternative drugs for the treatment of this infection. Halofantrine is a phenanthrene methanol, it was highly active against multi-drug resistant isolates of *P. falciparum* in preclinical studies (Schmidt *et al,* 1978; Desjardins *et al,* 1979) with no significant toxicity at doses proposed for use in humans. Clinical studies demonstrated that halofantrine is highly effective against multi-drug resistant falciparum malaria when administered in at least three doses over one day (Rinehart *et al,* 1976; Cosgriff *et al,* 1982; Boudreau *et al,* 1988; Watkin *et al,* 1988). With the light of these data, it is therefore important to assess the efficacy of halofantrine in an area with well documented drug resistant *P. falciparum.* We have carried out a study to investigate safety and efficacy of halofantrine hydrochloride compared to mefloquine in the treatment of male patients with acute infection of *P. falciparum.*

MATERIALS AND METHODS

The study was a randomized prospective comparative trial of halofantrine hydrochloride tablets (250 mg/tablet) and mefloquine.

Patients

Fifty-five male patients with acute uncomplicated falciparum malaria (asexual form parasitemia of less than 5%), aged between 15 to 60 years and weight range 45 to 60 kg, with no history of liver or kidney diseases were recruited into the study. No other concurrent antimalarial drugs were taken during the study. Written informed consent to participate in the study was obtained from all patients.

Each patient underwent physical examination, routine blood examination and blood chemistry investigations, plain chest x-ray, urinalysis and

ECG. Plasma was taken for baseline antimalarials *ie* quinine, mefloquine and halofantrine. All patients were admitted into the Bangkok Hospital for Tropical Diseases for forty-two days.

Treatment

The patients were randomized and paired according to geographical areas (*ie* eastern, western and others) to receive oral dosage of either three doses of 500 mg halofantrine (250 mg/tablet) at 6 hour intervals or Lariam® 750 mg followed by 500 mg 6 hours apart, the additional dose of 250 mg was given 6 hours later to those with body weight of greater than 60 kg. The drug was administered with a glass of water under supervision.

Patients who had RI, RII and RIII response were treated with conventional antimalarial *eg* quinine 500 mg base, 8 hourly and tetracycline 250 mg four times a day for 7 days.

Parasite count

Parasite count was performed twice daily until negative, then once daily until day 42.

Hematological and biochemical investigations

Blood examination and biochemistry were done on day 0, day 2, day 4, day 7 then weekly until day 42.

***In vitro* sensitivity test**

In vitro sensitivity tests for chloroquine, quinine, quinidine and mefloquine were performed prior to drug administration.

Adverse effects

All adverse reactions during the study were recorded with the date and time when they occurred and disappeared. The severity was grading into 1, 2 and 3. These changes included gastro-intestinal, central nervous, cardiovascular, dermatological, hematological systems and other changes possibly attributed to halofantrine or mefloquine.

Vomiting and diarrhea: frequency on day 0 (minute or hour after dosing) day 1, day 2 day 3 and day 4 was recorded.

Itching/skin rash: history of itching/skin rash after mefloquine and halofantrine, intensity and duration of rash were recorded.

Blood pressure (BP) measurements were performed at 4 hour-interval (supine, sitting and standing) during the first week then daily (supine) until day 42.

Halofantrine concentrations

Pharmacokinetics of halofantrine were studied in 10 patients, the results will be presented elsewhere. Plasma concentrations of patients who had RII were measured and compared to those of sensitive response.

Halofantrine analysis

The plasma concentrations of halofantrine and its main metabolite were analysed by HPLC (Milton *et al,* 1988).

Statistical analysis

Student's *t*-test was used.

Data analysis

Minimum inhibitory concentrations (MIC:*in vitro* sensitivity test) of chloroquine, quinine, quinidine and mefloquine between the eastern and the western part of the country were compared.

Only those patients who completed a 42-day follow-up were evaluated for efficacy assessment and rate of recrudescence. All patients receiving treatment were evaluated for safety. Clinical evaluation were based on parasite clearance time, fever clearance time, recrudescent rate, incidence, frequency and severity of adverse effects and incidence of abnormal laboratory observations.

RESULTS

Fifty-five patients were included in the study. Twenty-eight received three doses of 500 mg halofantrine and 27 had mefloquine 750 mg followed by 500 mg 6 hours apart (there were 4 patients who had body weight of more than 60 kg received additional 250 mg of mefloquine at 6 hours later). Five patients (three from halofantrine and two from mefloquine group) were excluded from the analysis for efficacy and recrudescent rate due to an incomplete 42-day follow-up.

Admission clinical data, baseline laboratory findings were comparable in both groups (Table 1).

No significant drug related changes were seen in any of the hematological parameters nor biochemical investigations.

In vitro sensitivity

The MIC of chloroquine and mefloquine were higher in the eastern than the western part ($p < 0.05$, Table 2). However, the MIC for quinine and quinidine were similar in both parts of the country.

Clinical response

Twenty-three patients in halofantrine group had a good initial response with fever and parasite clearance times of 54.8 ± 26.2 hours and 75.9 ± 20.4 hours, respectively. Nine patients had RI type of response and two had RII response. Both patients with RII response had vomiting 2 to 6 times after drug administration. Plasma concentrations were measured in these two patients. The plasma concentrations of halofantrine were relatively low in the patient who vomited 6 times in comparison to the mean values obtained from patients with sensitive response (Fig 1). The cure rate was 56%. Analysis of the efficacy by geographical area were 28.57%, 57.14% and 14.28% for S, RI and RII response, respectively for the eastern border (where highly multi-drug resistant strains of falciparum exist). This finding is in contrary to the western side of the country where there was much higher S type of response *ie* 87.5% and only 12.5% of RI response with no RII (Table 3).

Twenty-one patients in mefloquine group had S type of response. Fever and parasite clearance times were 57.0 ± 30.1 and 79.9 ± 26.2 hours, respectively. Three patients showed RI response and one had RII. The cure rate was 84%. Analysis of the efficacy by geographical area were 78.57%, 14.28% and 7.14% for S, RI and RII response, respectively in the eastern border. The efficacy in western part did not differ strikingly as that found in halofantrine group *ie* 87.5%, 12.5% for S and

Table 1

Clinical data.

	Halofantrine	Mefloquine
Age (years)	26.8 ± 9.6	28.5 ± 12.1
Weight (Kg)	54.8 ± 6.9	53.3 ± 6.9
Hematocrit (%)	35.2 ± 6.8	35.8 ± 6.7
Parasitemia (/mm^3)	19994	14421
(range)	3160-146400	3460-89400
FCT (hours)	54.8 ± 26.2	57.0 ± 30.1
PCT (hours)	75.9 ± 20.4	79.9 ± 26.2

Table 2

Mean MIC values of chloroquine, quinine, quinidine and mefloquine in *in vitro* sensitivity testing.

	Eastern MIC (pmole/50µl)	Western MIC (pmole/50µl)
Chloroquine	50*	28
Quinine	165	106
Quinidine	58	53
Mefloquine	15**	7

* = Significantly different from Western.
** = Significant different from Western.

Table 3

Clinical response by geographical area.

Area	Halofantrine				Mefloquine			
	N	S	RI	RII	N	S	RI	RII
East	14	4	8	2	14	11	2	1
%		29	57	14		79	14	7
West	8	7	1	0	8	7	1	0
%		88	12	0		88	12	0
Others	3	3	0	0	3	3	0	0
%		100	0	0		100	0	0
Total	25	14	9	2	25	21	3	1
%		56	36	8		84	12	4

Table 4

Comparison of the adverse effects in halofantrine and mefloquine.

	Halofantrine	Mefloquine
Vomiting	22%	41%
Diarrhea	33%	26%
Dizziness	37%	21%
Orthostatic hypotension	33%	14%
Black-out	11%	7%

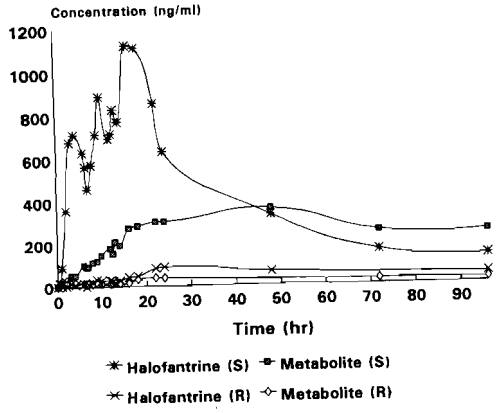

Fig 1—Plasma concentration of halofantrine and its metabolite.

RI respectively.

Adverse effects

The common adverse effects found in the halofantrine group were vomiting (22%), diarrhea (33%), dizziness (37%), orthostatic hypotension (33%) and black-out (11%). The incidence of vomiting was higher in mefloquine group *ie* 41%; however, other adverse effects such as diarrhea, dizziness, orthostatic hypotension and black-out were noticed more often with halofantrine (Table 4).

DISCUSSION

In general, halofantrine was well tolerated in the present study. Halofantrine has no effect on hematological profiles. There was no significant drug-related effect on either creatinine or bilirubin levels. There was however higher incidence of orthostatic hypotension and black-out when compared to mefloquine. Attention should be made to cardiovascular effects in future studies. Neuropsychiatric reactions have not been reported with halofantrine, based on 18 studies conducted over the last 16 years with the first (phase III) clinical trial in 1982. This may be an advantage over mefloquine in the treatment of *P. falciparum* malaria in the areas where parasites are still sensitive to halofantrine.

This clinical trial shows that on the western part of Thailand, oral halofantrine hydrochloride at 500 mg for 3 doses at 6 hours interval is equally as effective as mefloquine 1,250 mg (fractionated dose) in the treatment of acute uncomplicated malaria. The cure rate was 87.5% with comparable parasite and fever clearance times of that obtained from mefloquine. However, contradictory results were obtained from the eastern part of the country. Halofantrine cured only 28.57% in comparison to 78.57% with mefloquine. It was shown that strains of *P. falciparum* were resistant to multiple antimalarial drugs to a much higher degree near the eastern than near the western border (Table 2 and Thaithong, personal communication). It is therefore reasonable to suggest that halofantrine is highly effective in areas where less drug resistant strains of *P. falciparum* exist.

The low cure rate of 56% in this study was not expected. A previous study carried out in Thailand with the same dosage regimen showed the cure rate of 89% (Boudreau *et al*, 1988). This study was carried out during 1982-1983 in an eastern provincial hospital. Halofantrine was found to be equally effective in the treatment of chloroquine resistant falciparum malaria. Mefloquine cured 88% of the patients with falciparum malaria at a dose of 19 mg/kg and 97% at a dose of 27 mg/kg in that study. The present study took place in 1989; therefore, it is possible that in the intervening period, increased halofantrine resistance has developed.

A more recent study (Chitchang *et al*, 1989) was performed in the Thai Army Hospital, Bangkok. There were 84 Thai soldiers from the eastern border of Thailand included in the study during 1986-1987. The result showed a very impressive cure rate of 97% with 28 day follow-up. The extended 42 day follow-up in the present study did not contribute to the difference in efficacy, as most recrudescences occurred within 28 days. there was however, one case which recrudesced beyond 28 days, *ie* day 32. The possible explanations for the difference in efficacy are 1) the population examined in the present study was highly selective; 2) the parasites develop resistance to halofantrine rapidly since the present study was carried out only one year after the previous study but the sensitive response was strikingly lower (97% versus 44%); 3) variability of absorption which resulted in low levels of halofantrine. As it was shown in the present study that one of the two RII type response cases had very low plasma halofantrine concentrations, so that the failure must be due to incomplete absorption rather than genuine resistance. It has been noted in one study that clinical failure had much lower serum halofantrine levels than those with sensitive response (Boudreau *et al*, 1988). Therefore it is essential to compare the plasma halofantrine concentrations in cured and failed cases to document the genuine resistant falciparum strains to halofantrine (*ie* if the plasma halofantrine concentrations are very low in recrudescent patients then it is not the problem of resistance but of absorption).

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