

A CLINICAL TREATMENT TRIAL OF HALOFANTRINE AGAINST  
*P. falciparum* MALARIA ON THE  
THAI-KAMPUCHEAN BORDER

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BACKGROUND : For the effective treatment of malaria in outpatient programs, it is necessary to have a single-dose or short-term therapy that is nearly 100% curative. Divided dose therapy over 7-10 days is generally not effective in outpatient programs, since patient compliance falls off rapidly once the symptoms abate. Chloroquine, given over a 3 day period, was, and in many parts of the world still is, the therapeutic mainstay of antimalarial programs.

The combination of sulfadoxine and pyrimethamine which has been effective as a single dose, took the place of chloroquine in the outpatient treatment of falciparum malaria, as chloroquine-resistance spread especially in Southeast Asia. With the development of resistance to the sulfadoxine-pyrimethamine combination in Thailand, especially along the Thai-Kampuchean border, these areas are left without any effective single dose or short therapy drug regimens. Mefloquine has proven effective in a single dose, but is not yet commercially available.

The 9-phenanthrenemethanols were first evaluated in human subjects during the Second World War, but with the early success of chloroquine further drug development was halted until the early seventies when chloroquine resistance developed in Southeast Asia. Halofantrine was the most efficacious and least toxic of three phenanthrenemethanol compounds of this class tested in animal studies (1). In the Aotus monkey halofantrine equalled chloroquine in activity against chloroquine sensitive strains of *P. falciparum* but was equally active against chloroquine, pyrimethamine or quinine resistant strains. The drug however was not effective when given as a single dose, even in the monkey model, perhaps due to poor gastrointestinal absorption of this poorly water soluble agent.

Preclinical toxicity studies pinpointed the target organs as the lymphoid tissues, the kidney, GI tract, bone marrow and skeletal muscle. These were effected in the dog at 15 mg/kg/day or greater for 28 days (2). Single doses of greater than 2-3 gm/kg were necessary to kill mice and rats. So it appeared to be fairly safe drug. Toxicity, in Phase I studies in men, was seen only at a daily dose > 1,250 mg and was limited to abdominal cramps, nausea and diarrhea (3).

In Phase II efficacy studies against multi-drug resistant *P. falciparum* malaria, in malaria induced by blood inoculation of volunteers, halofantrine cured 24/27 (90%). The 3 recrudescences in this Phase II study occurred when a single dose was given (1,000 mg and 1,500 mg). At divided doses in a single day the drug was 100% curative in 14 patients (1,000-1,500 mg). Only 15% experienced gastrointestinal side effects post dosing. The mean parasite clearance time in these patients was rapid at 49 hrs (4). Therefore, with high hopes for the success of field trials an efficacy evaluation of halofantrine in Thailand was designed.

*P. falciparum* malaria in the Cambodian border area was selected as a severe but reliable indicator of the drug's effectiveness.

#### METHODS :

*Design* : Eighty patients were entered in a randomized double blinded clinical drug trial comparing the efficacy of single day treatment with halofantrine or mefloquine. The site was Ft. Taksin Marine Hospital in Chantaburi, Southeastern, Thailand. The period included in this report was June 1982 - April 1983.

#### *Patient selection criteria were:*

1. All marines stationed along the Thai-Cambodian border presenting with parasitemia  $< 100,000/\text{mm}^3$ .
2. 21 - 50 years of age.
3. Willing to give informed consent, willing to take an investigational drug to treat their malaria and willing to remain hospitalized for 21 days.
4. No complicating factors such as protracted vomiting, markedly decreased renal output, hypotension or cerebral malaria.
5. No concomitant disease.
6. No mixed infections.

#### *The drug doses utilized were:*

- 40 patients - mefloquine 1,500 mg single dose p.o.
- 20 patients - halofantrine 1,000 mg, and 6 hrs later 500 mg p.o.
- 20 patients - halofantrine 500 mg q 6 hr x 3 p.o.

At patient number CH 30, the double blinding of the study was changed to patient blinding due to the high incidence of treatment failures and alteration was made in the halofantrine dosing regimen from 1,000 mg followed by 500 mg at 6 hr to 500 mg q 6 hr x 3.

RESULTS :

1. Mefloquine has still proven 95% effective (cure in 38/40 patients)

- 1 RII
- 1 RI day 39

2. Halofantrine doses combined cured : 76%

Halofantrine 1,000 mg followed at 6 hr by 500 mg cured (13/20) = 65%

- a. 1 RII (retreated on day 7)  
6 RI (1 day 14, 3 day 21, 2 day 27)
- b. Parasite clearance time - 83 hrs  
mean (n = 19)  
Fever clearance time - 63.8 hrs  
mean (n = 17)
- c. The *in vitro* drug sensitivity testing performed on the recrudescant patients and the successfully treated and cured patients revealed no significant difference between the halofantrine ID 50 in 7 recrudescant patients of  $2.30 \pm .66$  mg/ml and the halofantrine ID 50 of 18 other patients in the study of  $1.51 \pm 0.32$ .

Halofantrine 500 mg q 6 x 3 (cure 19/20) = 95%

- a. 1 RI recrudescence - day 12
- b. Parasite clearance time - (mean n = 20) = 73.6 hrs  
Fever clearance time - (mean n = 20) = 51.4 hrs

See (Table 1) and (Table 2)

3. Side effects were not significantly different with the two different drugs or the two different drug regimens. However there is a trend toward less diarrhea and more asymptomatic patients with halofantrine 500 mg q 6 hr x 3 than with mefloquine or halofantrine 1,000 mg followed 6 hr later by 500 mg. (Table 3).

4. The parasite clearance times and fever clearance times were not significantly different between groups. The initial parasite count in the 1,000-500 mg group was significantly greater than the 500 q 6 x 3 group.

5. The patients' immune status in both drug groups was comparable. (Figure 1).

6. These are preliminary results on a study 66% complete (80/120 patients).

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Table 1.

	IAC (st. dev.)	PCT (st. dev.)	FCT (st. dev.)
HALO 1	n = 20 42,707 (31,050) sdm = 6,943	n = 19 83 (22.3) sdm = 5.1	n = 17 63.8 (46.3) sdm = 11.2
HALO 2	n = 20 22,650 (17,490) sdm = 3,910	n = 20 73.6 (16.8) sdm = 3.8	n = 20 51.4 (31.4) sdm = 7.0
MEFL	n = 40 35,437 (31,777) sdm = 5024	n = 38 78.5 (25.2) sdm = 4.1	n = 38 53.3 (29.2) sdm = 4.7

HALO 1 = Halofantrine 1000 mg + 500 mg  
 HALO 2 = Halofantrine 500 mg + 500 mg + 500 mg  
 sdm = standard deviation of mean

Table 2.

## Resistant Cases

Halofantrine

	PCT (hr)	FCT (hr)	IPC/mm <sup>3</sup>	GI intolerance	Drug of Recrudescence
CH 14	89.5	168	73,372	None	RI day 27
CH 15	77	56	63,163	Diarrhea	RI day 14
CH 18	-	230	92,213	Diarrhea, nausea	RI retreated day 7
CH 20	132	19	24,700	Vomitted 20 minutes post 1st dose	RI day 21
CH 24	72	56	98,023	None	RI day 21
CH 34	94	28	47,040	Diarrhea, epigastric pain	RI day 21
CH 36	78	44	26,620	Epigastric pain	RI day 27
CH 57	94	140	27,639	None	RI day 12

Mefloquine

CH 12	-	56	70,799	Vomitted 7 hrs post-dose, nausea abdominal	RII
CH 64	71	22	20,003	Diarrhea	RI day 39

Table 3

Incidence of Post-dosing Side Effects

	Mefloquine 1500 mg Single dose	Halofantrine 1000 mg 6 hrs later 500 mg	Halofantrine 500 mg q 6 hr x 3
Nausea	20% (8/40)	20% (4/20)	30% (6/20)
Vomitting	15% (6/40)	20% (4/20)	25% (5/20)
Diarrhea	33% (13/40)	30% (6/20)	10% (2/20)
Abd. pain	26% (9/40)	20% (4/20)	10% (2/20)
No symptoms	30% (12/40)	30% (6/20)	50% (10/20)

No significant differences in side effects from one drug group to another.

FIGURE 1

