# HALOFANTRINE IN THE TREATMENT OF ACUTE UNCOMPLICATED FALCIPARUM MALARIA IN THE PHILIPPINES

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**Abstract.** In an open clinical trial, thirty patients 14 to 44 years old and with acute uncomplicated falciparum malaria were given halofantrine hydrochloride 500 mg (2 tablets) 6-hourly for 3 doses, a total dose of 1500 mg. All 30 patients were cured, with a mean asexual parasite clearance time of 47.6 hours and mean fever clearance time of 36.6 hours. Post-dosing side-effects occurred in 6 patients consisting of mild to moderate headache, dizziness and abdominal muscle spasm. Drug-induced hemolysis did not occur in two G6PD deficient patients. Twenty-three out of 28 isolates tested (82%) were resistant to amodiaquine, 3 (11%) were resistant to the sulfadoxine-pyrimethamine combination, and all were sensitive to chloroquine, quinine and mefloquine by *in vitro* microtests. The study confirms the efficacy of halofantrine hydrochloride as a blood schizonticide in falciparum malaria.

## INTRODUCTION

The emergence of refractory strains of *Plasmodium falciparum* to treatment with the 4-aminoquinolines brought forth the need for alternative antimalarials. Although chloroquine resistance and multidrug-resistance is at a low level in the Philippines (Salazar, 1989) increasing resistance to amodiaquine, a related compound (Watt *et al,* 1986; Long *et al,* 1987), the sulfadoxine-pyrimethamine combination (Malaria Control Service, personal communication; Watt *et al,* 1987), quinine and mefloquine (Smrkovski *et al,* 1982a; 1982b; 1985) has been observed in recent years. In view of this, clinical trials were conducted by several other workers using existing and new drug combinations.

Halofantrine hydrochloride, a phenanthrenemethanol, is one of 250,000 separate chemical entities examined for antimalarial activity under the drug development program of the Walter Reed Army Research Institute of Research in the US (Rhinehart *et al,* 1976). Earlier clinical trials were done in Thailand, Africa and South America. The present study aimed to test the efficacy of the drug as a blood schizontocide in Filipino patients.

## MATERIALS AND METHODS

The study is an open clinical trial involving thirty patients over 12 years old, weighing more than 40 kg, with acute, uncomplicated falciparum malaria and asexual parasitemia of at least 1000/mm$^3$. Pregnant or lactating women, those who have taken antimalarials in the past two weeks, those with evidence of severe disease (WHO 1986), mixed infections, and patients for whom oral therapy was not possible were excluded. Informed consent was obtained prior to enrolment. The study was conducted at the Research Institute for Tropical Medicine (RITM) hospital from September 1988 to April 1989. All patients were hospitalized throughout the 28-day period of observation.

Pre-treatment procedures included history-taking, complete physical examination, Dill-Glazco and lignin tests for antimalerials in urine, routine urinalysis, hematologic and biochemical

Table 1

Parasite and fever clearance time.

| Patient no. | Parasite count (no/mm$^3$) at treatment | highest | Clearance parasite | Time (hours) fever |
|---|---|---|---|---|
| 1 | 5,856 | 5,856 | 48 | A* |
| 2 | 1,427 | 3,320 | 48 | A |
| 3 | 5,190 | 8,495 | 48 | 11 |
| 4 | 5,922 | 8,571 | 48 | A |
| 5 | 7,926 | 8,971 | 48 | A |
| 6 | 4,566 | 6,086 | 48 | 48 |
| 7 | 1,887 | 4,353 | 48 | 43 |
| 8 | 72,480 | 72,480 | 54 | 60 |
| 9 | 9,711 | 19,902 | 48 | 24 |
| 10 | 1,307 | 1,531 | 48 | A |
| 11 | 1,861 | 4,320 | 54 | 15 |
| 12 | 39,480 | 24,275 | 48 | 48 |
| 13 | 1,249 | 6,751 | 30 | 23 |
| 14 | 1,075 | 2,766 | 48 | A |
| 15 | 2,058 | 2,058 | 48 | A |
| 16 | 5,112 | 10,098 | 48 | A |
| 17 | 10,851 | 11,218 | 48 | 24 |
| 18 | 9,932 | 14,275 | 48 | 24 |
| 19 | 15,146 | 15,146 | 54 | 47 |
| 20 | 9,739 | 30,424 | 48 | 39 |
| 21 | 25,876 | 25,876 | 48 | 24 |
| 22 | 2,483 | 2,483 | 48 | A |
| 23 | 6,815 | 6,815 | 48 | 72 |
| 24 | 2,549 | 7,529 | 54 | 13 |
| 25 | 23,320 | 23,320 | 54 | 41 |
| 26 | 13,047 | 58,224 | 72 | 72 |
| 27 | 1,249 | 1,636 | 24 | A |
| 28 | 6,448 | 9,055 | 48 | 24 |
| 29 | 6,600 | 10,235 | 48 | 32 |
| 30 | 3,725 | 3,843 | 24 | 48 |
| Mean | 10,163 | 13,664 | 47.6 | 36.6 |
| SD | 14,278 | 15,861 | 8.6 | 17.7 |
| Range | 1,075-72,480 | 1,531-72,480 | 24-72 | 13-72 |

*A-afebrile at treatment

determinations, including G6PD assay. The parasites were counted in Giemsa-stained peripheral blood smears.

Halofantrine hydrochloride (Halfan, Smith-Kline Beecham) came as uncoated tablets containing 250 mg halofantrine. The drug was administered orally 500 mg (2 tablets) 6-hourly for 3 doses. Concomitant treatment of other drugs specially those with antimalarial activity was avoided. Clinical and laboratory assessments (routine hematology, urinalysis and hepatic and renal function tests) were performed on days 0 to 7, 14, 21 and 28. Patients were evaluated 2 hours after each dose, then daily for 7 days to document any adverse effects of the drug. Oral temperature

was taken every 4 hours until the patients became afebrile, and parasite counts performed twice daily for the first 7 days and on days 14, 21 and 28.

Assessment of response to treatment was based on asexual parasite clearance time and time taken to become afebrile (oral temperature maintained at < 37.5°C for at least 48 hours). Overall patient response was evaluated according to the WHO criteria of S (sensitivity), or RI, RII, RIII (levels of resistance). *In vitro* drug-sensitivity testing using the WHO microtest method (Rieckmann *et al,* 1978) was done to assess sensitivity to chloroquine, amodiaquine, mefloquine, quinine and sulfadoxine-pyrimethamine. Results were interpreted as sensitive (S) or resistant (R) in terms of the cut-off point for sensitivity as follows: chloroquine 4.0 pmol; amodiaquine 2.0 pmol; mefloquine 32.0 pmol; quinine 128 pmol; sulfadoxine-pyrimethamine 1000 pmol.

## RESULTS

All 30 evaluable patients enrolled in the study came from different malaria endemic areas in the country. At the onset of treatment, 10 patients were afebrile and had no recorded fever during the treatment period. The mean maximal body temperature was 38.4°C before treatment (range 36.5 to 40.2°C), resulting in a mean fever clearance time of 36.6 hours post-treatment (range 11 to 72 hours), excluding the 10 afebrile patients (Table 1).

The mean asexual parasite count prior to treatment was 10,145 $mm^3$ (range = 1,075 to 72,480/$mm^3$) resulting in a mean parasite clearance time of 47.6 hours (range 24 to 72 hours) post-treatment. None of the patients recrudesced during the 28-day follow-up period. Six patients had gametocytes up to day 28 but were treated with primaquine upon discharge. On admission, only one patient had hepatomegaly with a liver span of 15 cm and 19 had splenomegaly. All reduced spontaneously within 28 days.

Hemoglobin values returned to normal or close to normal values except for 9 patients whose Hgb values remained below normal by day 28 (Table 2). Platelet counts remained normal throughout the study in all patients. RBC and WBC counts improved gradually after treatment.

Eosinophilia (ie eosinophil counts greater than $0.45 \times 10^9$/l) was noted in 29 out of 30 patients. Eosinophil counts ranged from 0 to $2.912 \times 10^9$/l (mean = $0.48 \times 10^9$/l). Seven had elevated eosinophil counts on initial CBC, 5 of whom had intestinal parasites. Eosinophilia was noted as early as the first day after the drug was given (day 1), persisting until day 28 in 25 patients. This was found to be temporary with normalization of eosinophil counts in 2 patients 2 months after the drug intake. Serum chemistry findings are presented in Table 3. Ten patients had no biochemical abnormalities. Alkaline phosphatase remained persistently elevated in 6 patients up to day 28 ranging from 56.7 to 165 units/l (NV = 13-50 units/l). Renal function tests (BUN and creatinine) were normal in all patients pre- and post-treatment. SGPT was normal in all patients on admission, but was slightly above normal in 2 patients by day 28 (37.9 units/l in patient 4 and 22.1 units/l in patient 14). Total bilirubin was elevated in 7 patients on admission, but returned to normal by day 28 in all patients. All other hematological and biochemical parameters were within normal limits.

There were no manifestations of any cardiovascular problems pre- and post-treatment in 29 patients. One patient, with a previous history of hypertension, had elevated blood pressure on days 19 and 20 (max BP = 210/100), but was immediately controlled by nifedipine. Electrocardiogram and chest X-ray were normal.

Glucose-6-phosphate dehydrogenase (G6PD) tests showed 2 patients to be deficient. Patient 22 had a G6PD value of 2.3 units/g Hb. While patient 23 had a value of 0 (NV = 4.6-13.5 U/g Hb). No evidence of hemolysis was noted on serial monitoring of urinalysis and reticulocyte counts.

Six patients experienced mild to moderate side effects manifested as headache, abdominal pain, dizziness, and abdominal muscle spasm, noted within 2 hours after drug intake. No patient complained of any side effects severe enough to warrant discontinuation of treatment.

Table 4 shows the results of *in vitro* drug sensitivity tests done on 28 patients. All 28 isolates were sensitive to chloroquine, quinine, and mefloquine. Resistance to amodiaquine was noted in 22 isolates,

Table 2

Hematologic findings in 30 evaluable patients treated with halofantrine hydrochloride at RITM hospital.

| | D00 | D07 | D14 | D21 | D28 |
|---|---|---|---|---|---|
| Hemoglobin (gm/dl) | | | | | |
| NV: M = 13-18; F = 11-16 | | | | | |
| mean | 11.53 | 11.58 | 11.97 | 12.74 | 13.02 |
| SD | 2.21 | 1.30 | 1.20 | 1.19 | 1.29 |
| range | 8-17.2 | 9-14.3 | 9.8-14.3 | 10.3-16.3 | 10.4-17.3 |
| Hematocrit | | | | | |
| NV: M = 0.42-0.51 | | | | | |
| F = 0.37-0.47 | | | | | |
| mean | 0.34 | 0.35 | 0.36 | 0.38 | 0.39 |
| SD | 0.08 | 0.04 | 0.04 | 0.03 | 0.04 |
| range | 0.04-0.51 | 0.26-0.4 | 0.28-0.43 | 0.3-0.45 | 0.31-0.51 |
| RBC count (x $10^{12}$/l) | | | | | |
| NV: M = 4.6-5.2 | | | | | |
| F = 4.4-5.0 | | | | | |
| mean | 3.87 | 3.88 | 3.98 | 4.17 | 4.28 |
| SD | 0.76 | 0.48 | 0.45 | 0.46 | 0.54 |
| range | 2.73-6.3 | 2.98-5.2 | 3.2-4.95 | 3.3-5.12 | 3.3-5.9 |
| WBC count (x $10^9$/l) | | | | | |
| NV: 5-10 | | | | | |
| mean | 6.52 | 6.79 | 7.63 | 8.48 | 8.28 |
| SD | 1.22 | 1.50 | 1.69 | 2.14 | 1.67 |
| range | 4.25-9.6 | 3.57-10.4 | 5.1-12 | 4.75-13.55 | 4.31-11.65 |
| Absolute eosinophil count (x $10^9$/l) | | | | | |
| NV: up to 0.45 | | | | | |
| mean | 0.18 | 0.57 | 0.72 | 0.96 | 1.02 |
| SD | 0.17 | 0.42 | 0.58 | 0.67 | 0.67 |
| range | 0-0.511 | 0.-1.5 | 0.-2.912 | 0.128-2.88 | 0.143-2.30 |
| Platelet count (x $10^9$/l) | | | | | |
| NV: 140-430 | | | | | |
| mean | 255.2 | 252.9 | 257.97 | 268.43 | 275.90 |
| SD | 46.73 | 42.87 | 39.09 | 37.89 | 39.10 |
| range | 180-396 | 194-390 | 200-380 | 210-384 | 206-388 |

to sulfadoxine-pyrimethamine in 2 isolates, and to both amodiaquine and sulfadoxine-pyrimethamine in 1 patient.

## DISCUSSION

This clinical trial shows that halofantrine is highly efficacious for the treatment of falciparum malaria with a total dose of 1500 mg administered 500 mg 6 hourly. The rapid parasite and fever clearance times were comparable with those observed in previous studies (Cosgriff *et al,* 1982; Boudreau *et al,* 1988). The peak plasma concentration of halofantrine is achieved in 6 hours, and 12 hours for its N-desbutyl halofantrine metabolite, with an elimination half-life of 1-2 days and 3-5 days, respectively (Milton *et al,* 1989). Although *in vitro* drug sensitivity tests to halofantrine nor

Table 3

Serum chemistry of 30 halofantrine-treated patients.

| | D00 | D07 | D14 | D21 | D28 |
|---|---|---|---|---|---|
| SGPT (units/l) | | | | | |
| NV: up to 16.8 | | | | | |
| mean | 6.52 | 7.71 | 8.28 | 7.83 | 7.82 |
| SD | 3.37 | 4.95 | 8.06 | 6.95 | 7.13 |
| range | 1.4-16.3 | 1.4-20.2 | 1.4-20.2 | 1.4-45.1 | 0-37.9 |
| Alkaline phosphatase (units/l) | | | | | |
| NV: 13-50 | | | | | |
| mean | 46.73 | 40.76 | 45.03 | 47.3 | 49.58 |
| SD | 16.36 | 11.21 | 12.92 | 15.56 | 27.49 |
| range | 24-89.2 | 20.8-77.5 | 25.5-75.8 | 26.7-81.7 | 17.5-165 |
| Total Bilirubin (mg/dl) | | | | | |
| NV: 0.099-1.199 | | | | | |
| mean | 1.32 | 0.64 | 0.8 | 0.79 | 0.98 |
| SD | 1.98 | 0.9 | 1.19 | 1.01 | 2.28 |
| range | 0.3-11.7 | 0.2-5.4 | 0.29-7.1 | 0.17-6.1 | 0.28-13.2 |
| BUN (mg/dl) | | | | | |
| NV: 8-20 | | | | | |
| mean | 11.28 | 8.32 | 8.66 | 9.87 | 8.28 |
| SD | 4.06 | 2.29 | 2.26 | 3.41 | 2.57 |
| range | 3.64-19.8 | 5-15.12 | 5.04-12.61 | 1.01-17 | 5-15.12 |
| Creatinine (mg/dl) | | | | | |
| NV: up to 2 | | | | | |
| mean | 1.38 | 1.24 | 1.44 | 1.20 | 1.18 |
| SD | 0.33 | 0.45 | 0.78 | 0.23 | 0.25 |
| range | 0.63-1.8 | 0.31-3 | 0.59-10.9 | 0.6-1.6 | 0.59-1.5 |
| RBS (mmol/l) | | | | | |
| NV: 3.9-6.4 | | | | | |
| mean | 5.62 | 4.65 | 4.7 | 4.97 | 4.62 |
| SD | 1.26 | 1.28 | 1.22 | 1.01 | 1.37 |
| range | 3.6-8.25 | 3.4-6.5 | 3-8.4 | 3.72-8.1 | 3.7-7.9 |

plasma level determination of the drug were not done, there was no recrudescence during the 28-day follow-up, suggesting sensitivity to halofantrine and adequate blood levels. Individual variations in drug absorption and bioavailability has been reported to be responsible for the inadequate response to treatment in some cases (Boudreau *et al*, 1988; Gay *et al*, 1990).

The clinical and biological tolerance to the drug was good. Side effects were self-limiting. Eleven patients had elevated alkaline phosphatase on admission, which remained persistently above normal in 6 patients by day 28. We could not identify any underlying disease process to account for this biochemical abnormality. Eosinophilia, which was observed in almost all patients post-treatment, has not been reported elsewhere.

Our preliminary results indicate that this dosage is sufficient among Filipino patients. Its rapid schizontocidal activity and very short half-life makes it ideal for treatment in endemic areas with multi-drug resistant falciparum malaria.

Table 4

Results of *in vitro* drug sensitivity tests on *P. falciparum* isolates.

| Patient No. | Chloro | Amo | Quin | Meflo | Sulf-Pyr |
|---|---|---|---|---|---|
| 1 | S | S | S | - | S |
| 2 | S | R | S | S | S |
| 3 | S | R | S | S | S |
| 4 | S | R | S | S | S |
| 5 | S | R | S | S | S |
| 6 | S | R | S | S | R |
| 7 | S | R | S | S | S |
| 8 | S | R | S | S | S |
| 9 | S | S | S | S | S |
| 10 | S | S | S | S | R |
| 11 | S | S | S | S | R |
| 12 | - | - | - | - | - |
| 13 | - | - | - | - | - |
| 14 | S | R | S | S | - |
| 15 | S | R | S | S | S |
| 16 | S | R | S | S | S |
| 17 | S | R | S | S | S |
| 18 | S | R | S | S | S |
| 19 | S | R | S | S | S |
| 20 | S | R | S | S | S |
| 21 | S | R | S | S | S |
| 22 | S | R | S | S | S |
| 23 | S | R | S | S | S |
| 24 | S | R | S | S | S |
| 25 | S | R | S | S | S |
| 26 | S | R | S | S | S |
| 27 | S | R | S | S | S |
| 28 | S | R | S | S | S |
| 29 | S | R | S | S | S |
| 30 | S | S | S | S | S |

S-sensitive
R-resistant
(-)-not done

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## REFERENCES

Boudreau EF, Pang LW, Dixon KE, *et al.* Malaria: treatment efficacy of halofantrine (WR 171,669) in initial field trials in Thailand. *Bull WHO* 1988; 66 : 227-35.

Cosgriff TM, Boudreau EF, Pamplin CL, Doberstyn EB, Desjardins RE, Canfield CJ. Evaluation of the

antimalarial activity of the phenanthrenemethanol halofantrine (WR 171,669). *Am J Trop Med Hyg* 1982; 31 : 1075-9.

Gay F, Bustos MDG, Caumes E, *et al.* Insuffisance d'une cure d'halofantrine sur un paludisme a *Plasmodium falciparum* chloroquinoresistant contracte en Sierra Leonne. *Ann Med Interne* 1990; 141 : 493.

Long GW, Watt G, Sy N, Buck RL, Sangalang RP, Ranoa CP. *In vitro* drug response of *Plasmodium falciparum* in the Philippines: Increased resistance to amodiaquine. *Southeast Asian J Trop Med Public Health* 1987; 18 : 202-6.

Milton KA, Edwards G, Ward SA, Orme MLE, Breckenridge AM. Pharmacokinetics of Halofantrine in man: effects of food and dose size. *Br J Clin Pharmacol* 1989; 28 : 71-5.

Rhinehart J, Arnold J, Canfield CJ. Evaluation of two phenanthrenemethanols for antimalarial activity in man: WR 122,455 and WR 171,669. *Am J Trop Med Hyg* 1976; 25 : 769-74.

Rieckmann KH, Sax LJ, Campbell GH, Mrema JE. Drug sensitivity of *Plasmodium falciparum:* an *in vitro* microtechnique. *Lancet* 1987; 1 : 22-3.

Salazar NP, The malaria situation in the Philippines: A Critique. *Technical Report Series No. 7.* Philippine Council for Health Research and Development. *Tech Rep Ser* 1989; 7 : 1-49.

Smrkovski LL, Buck RL, Alcantara AK, Rodriguez CS, Uylangco CV. *In vitro* mefloquine resistant *Plasmodium falciparum* from the Philippines. *Lancet* 1982a; 2 : 322.

Smrkovski LL, Buck RL, Rodriguez CS, Wooster Mt, Mayuga JL, Rivera D. Chloroquine and quinine resistant *Plasmodium falciparum* on the island of Mindoro, Philippines. *Southeast Asian J Trop Med Public Health* 1982b; 13 : 551-5.

Smrkovski LL, Buck RL, Alcantara AK, Rodriguez CS, Uylangco CV. Studies of resistance to chloroquine, quinine, amodiaquine and mefloquine among Philippine strains of *Plasmodium falciparum. Trans R Soc Trop Med Hyg* 1985; 79 : 37-41.

Watt G, Long GW, Padre L, *et al.* Amodiaquine less effective than chloroquine in the treatment of falciparum malaria in the Philippines. *Am J Trop Med Hyg* 1986; 36 : 3-8.

Watt G, Padre LP, Tuazon LR, Laughlin LW. Fansidar resistance in the Philippines. *Trans R Soc Trop Med Hyg* 1987; 81 : 521.

WHO. Severe and complicated malaria. *Trans R Soc Trop Med Hyg* 1986; 80 [Suppl] : 3.