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Malaria: treatment efficacy of halofantrine (WR 171,669) in initial field trials in Thailand*

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Halofantrine (WR 171,669) hydrochloride was administered orally to 82 patients infected with Plasmodium falciparum *malaria on the Thai–Kampuchean border between June 1982 and December 1983 in a randomized double-blind treatment trial which compared the efficacy of halofantrine with that of mefloquine. Halofantrine was curative with oral treatment on a single day in 65% of patients (13/20) who received 1000 mg followed 6 hours later by an additional 500 mg, and in 88% of patients (53/60) who received 500 mg every 6 hours for 3 doses. Mefloquine was curative in 88% of patients (22/25) given a single oral dose of 1000 mg and in 97% of patients (38/39) given a single oral dose of 1500 mg. The difference in cure rates between the 3-dose halofantrine regimen and either of the mefloquine regimens was not significant. The mean parasite clearance time for all regimens ranged from 75 to 84 hours. The mean fever clearance time for all four treatment groups was in the range 50–60 hours, with no significant differences between groups. Post-dosing side-effects in patients treated with halofantrine consisted of nausea, vomiting, abdominal pain and diarrhoea and were not significantly different from those treated with mefloquine. Halofantrine therefore appeared to be of comparable efficacy to mefloquine in the treatment of multidrug-resistant* P. falciparum *malaria.*

Halofantrine (WR 171,669) is a phenanthrene-methanol. Preclinical studies demonstrated that this compound was highly active against multidrug-resistant isolates of *Plasmodium falciparum* (*1–2*) and caused no significant toxicity at therapeutic dosages to be used in humans.[a]

Phase I clinical pharmacology studies of halofantrine in healthy male volunteers revealed no significant clinical or laboratory abnormalities when the drug was given orally in divided doses over 6 days up to a maximum total dose of 6 grams (*3*). Studies with single oral doses up to 2000 mg revealed mild transient elevations of aspartate aminotransferase (SGOT) and alanine aminotransferase (SGPT).[b,c] With both single and divided doses, a minority of subjects developed dose-related symptoms including anorexia, nausea, abdominal cramps, and light-headedness.

Pharmacokinetic studies of halofantrine in healthy male volunteers using oral doses from 750 to 2000 mg revealed no correlation between drug dose and maximum blood concentration measured by either high performance liquid chromatography (HPLC) for detecting halofantrine or radioimmunoassay (RIA) for detecting halofantrine and its metabolites. There was also no correlation between drug dose and the area under the drug concentration–time curve. These

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[a] LEE, C.-C. ET AL. Interim Report No. 65 (1972) and Interim Report No. 66 (1982), Midwest Research Institute, Kansas City, Missouri. *U S. Army Medical Research and Development Command Contract No. DAMD-49-193-MD-2759* and *No DAMD-49-192-MD-2759.* (Reports available, on request, from the Commander, U.S. Army Medical Research and Development Command, ATTN: SGRD-RMS, Fort Detrick, Frederick, MD 21701-5014, USA).

[b] ARNOLD, J. D. Continuation of Phase I study of WR 171,669: maximal single-dose tolerance. University of Missouri, Kansas City, Missouri, 1975. *U.S. Army Research and Development Command Contract No. DAMD-17-74-C-4004.*

[c] JOHNSON, J. A. ET AL. Continuation of single-dose level studies with orally administered WR 171,669: short-term safety and tolerance. Preliminary pharmacokinetics. Bio-Med, Inc., Washington, DC, 1980. *U.S Army Medical Research and Development Command Contract No. DAMD-17-75-C-5036.*

findings suggested erratic bioavailability of the drug formulation tested. Using the HPLC assay, the mean absorption half-life for the drug was 2.3 hours and the mean elimination half-life was 2.6 days. The volume of drug distribution appeared to be large and the rate of drug clearance high. There was considerable variability both in the absorption half-life and in the elimination half-life. Using the RIA method, the mean elimination half-life of the drug and its metabolites was 5.1 days. This longer elimination half-life, compared with the HPLC value, reflects the fact that the RIA is sensitive to a major pharmacologically active metabolite, *N*-desbutyl halofantrine, in addition to the parent drug.[d]

Phase II clinical pharmacology studies of halofantrine in non-immune subjects with blood-induced multidrug-resistant *P. falciparum* malaria revealed that the drug was effective when administered over 2 or 3 days as well as over a single day (*4*). Single-day oral treatment regimens of 250 mg every 6 hours or 500 mg every 12 hours were effective. Halofantrine also proved effective when given orally in an initial dose of 1000 mg followed by 500 mg 6 hours later. Post-dosing symptoms were similar to those encountered in phase I testing and were mild and transient in every case.

The following report is an extension of efficacy testing of halofantrine in an endemic area of multidrug-resistant falciparum malaria.

METHODS

Patient selection

Patients for these studies were members of the Royal Thai Marines or volunteer soldiers stationed along a 125-mile section of the south-eastern Thai-Kampuchean border. They presented in two ways. In the first nine months of the study, 62 symptomatic patients presented for diagnosis and treatment of malaria at Ft. Taksin Marine Hospital in Chantaburi. During the second nine months of the study, 88 patients either presented at Ft. Taksin or were selected during malaria screening programmes of Thai soldiers stationed in three malaria endemic areas along the Kampuchean border.

The patients were between 21 and 50 years of age and had no concomitant illness. All were willing to give informed consent, to take an investigational drug for treatment of malaria, and to remain hospitalized for 21 days. For entry into the study they were required to have an initial parasite count of 500 to 100 000 per mm^3 and to have no evidence of significant complications of malaria, such as prolonged vomiting or central nervous system involvement. Patients whose initial malaria smear showed mixed infections (vivax and falciparum) were not accepted into the study.

Hospitalization

Each patient was hospitalized in a non-malarious area for 21 days following drug treatment. Patients whose infection recrudesced were hospitalized for an additional 21 days following retreatment. At the time of discharge, they were allowed to return to their units. A thorough history was taken and physical examination performed on each patient at the time of admission and serially during hospitalization. Twice daily parasite counts with examination of both thick and thin blood smears were done for 5 days following treatment, or until the smears were parasite negative for 24 hours, and then weekly for 4 weeks (*5*). Haematocrits (erythrocyte volume fractions), platelet counts, white cell counts and differentials were done daily for 7 days and then weekly for 4 weeks. Serum quinine and sulfa levels were determined on admission by the methods of Cramer & Isaksson (*6*) and Rieder (*7*), respectively. Liver function tests and blood urea nitrogen (BUN) were measured on days 0, 3 and 7 of each patient's hospital course.

Antimalarial drug administration

Halofantrine was given orally as the hydrochloride salt (Lot AD) in the form of 250-mg, white gelatin capsules (Lot WRA-1-03181), manufactured by the University of Iowa in March 1981. The first 20 halofantrine patients were treated with 1000 mg of halofantrine and mefloquine placebo tablets at time 0, followed 6 hours later by 500 mg of halofantrine (HALO I group). The remaining 62 halofantrine patients were treated with 500 mg every 6 hours for 3 doses, together with mefloquine placebo tablets at time 0 (HALO II group).

Mefloquine was given orally as the hydrochloride salt (Lot AS), initially manufactured as 250-mg, white uncoated tablets (WRA-12-04-013) by Lafayette Pharmacal in January 1980. The tablets were coated in April 1982 by the University of Iowa for purposes of double-blinding. The first 40 mefloquine patients were given a single dose of 1500 mg (MEF I). The remaining 25 patients received a single dose of 1000 mg (MEF II). All patients who received mefloquine were also given halofantrine placebos as capsules, the number administered depending on the concurrent halofantrine dosing regimen.

[d] FLECKENSTEIN, L. ET AL. Pharmacokinetics and bioavailability of orally administered halofantrine (WR 171,669) in healthy volunteers. *Investigational New Drug Report 9847, Suppl. 10*, pp. 93–133 (1983). (Report available, on request, from the Director, Division of Experimental Therapeutics, ATTN: SGRD-UWM-C, Walter Reed Army Institute of Research, Washington, DC 20307-5100, USA).

Patient follow-up procedures

Patients were discharged from the hospital on day 21 provided they were asymptomatic, their physical examinations were normal, and their malaria smears were negative. Seven days after discharge (day 28) they returned to the hospital for a final follow-up visit involving a symptom history, physical examination, complete blood cell count, and malaria smear.

During the study, the patients' military units were screened for malaria every two weeks, so that any recrudescence in a protocol patient after his return to his unit would be detected. Patients who developed recurrent malaria within 28–35 days post-treatment were readmitted to the hospital and treated either with quinine sulphate 650 mg every 8 hours plus tetracycline hydrochloride 500 mg every 8 hours for 7 days. Two patients with a history of allergy to tetracycline were treated with a single dose of mefloquine hydrochloride 1000 mg.

Response to treatment

Drug treatment was considered curative if there was a clearance of *P. falciparum* parasitaemia and no recrudescence of falciparum malaria during the 28-day follow-up. Two hundred oil-immersion fields on a thick smear were read on each patient's slide. Quantification of parasites was per cubic millimeter calculated by counting parasites in a 5-μl volume of blood over a 3×15 mm area on the slide (*5*). WHO-recommended terminology was used to classify recurrences of malaria (*8*).

Additional parameters of drug efficacy were fever and parasite clearance times. The parasite clearance time was the time from drug administration until an examination of 200 fields on a thick smear revealed no parasites. Parasite counts were performed twice daily by experienced laboratory technicians. The fever clearance time was defined as the time from drug administration until the oral temperature remained 37 °C or less, and remained so for at least 24 hours. Temperatures were monitored every 4 hours during hospitalization. As the parasite and fever clearance in patients with an RII response to treatment only occurred after the administration of quinine and tetracycline, the clearance times on these patients were not included in the tabulations.

In vitro *parasite drug sensitivity testing*

All patients had a blood sample drawn prior to treatment and at the time of recrudescence for determination of *in vitro* parasite drug sensitivity (*9*). After the blood was drawn, the parasitized red blood cells were washed and cryopreserved in liquid nitrogen at the study site. Cryopreserved specimens were transported in liquid nitrogen to the Armed Forces Research Institute of Medical Sciences, Bangkok, at weekly intervals. The dose of antimalarial drug required to cause 50% inhibition of parasite growth (ID_{50}), as calculated by reduced uptake of radiolabelled thymidine in 24 h by the malaria parasite, was compared in selected study patients.

Sera obtained on days 0, 3 and 7 post-treatment were frozen at −20 °C and used for determination of halofantrine levels. Day 3 sera on halofantrine subjects have been analysed using a very sensitive HPLC assay (E. Lin, University of California, San Francisco, unpublished). Both the parent drug and active metabolite, *N*-desbutyl halofantrine, were measured. *N*-desbutyl halofantrine demonstrated antimalarial activity equivalent to halofantrine against *P. berghei* KBG 173 in mice (M. Heiffer, unpublished WRAIR report) and equivalent activity against chloroquine-sensitive (Camp) and chloroquine-resistant (Vietnam Smith) strains *in vitro*.[e]

Data analysis

Chi-square (χ^2) and Fisher's exact test were used to compare results expressed as proportions such as cure rates and symptom rates. Student's *t*-test was used to compare fever and parasite clearance times and halofantrine serum levels. The Mann-Whitney U test was used to compare initial parasite counts because of non-normal distribution of the data. One-way analysis of variance was used to compare study entrance parameters such as liver enzymes, blood urea nitrogen, haematocrit, WBC and platelet counts, age and previous malaria infections. The paired *t*-test was used to compare the pretreatment blood chemistry and haematology values with those post-treatment within each drug group.

RESULTS

Comparability of treatment groups

Comparison of patients in each treatment group for the parameters of weight, age, and drug dose on a mg/kg basis revealed no significant differences by analysis of variance (ANOVA) except where the mefloquine dose was reduced. There was no significant difference by ANOVA between the 4 drug groups in admission values of SGOT, SGPT, total bilirubin, alkaline phosphatase, BUN or haematocrit. The mean number of days ill prior to admission to the study

[e] Comparison of halofantrine and its *N*-desbutyl analog, WR 178,460, by means of an *in vitro* antimalarial assay. *Investigational New Drug Report 9847, Supplement #8*, pp. 62–68. (Report available, on request, from the Director, Division of Experimental Therapeutics, ATTN: SGRD-UWM-C, Walter Reed Army Institute of Research, Washington, DC 20307-5100, USA).

was 5.3 and 5.1 days, respectively, in the 2-dose halofantrine group (HALO I) and 1500-mg mefloquine group (MEF I), but 3.5 days and 3.7 days, respectively, in the 3-dose halofantrine group (HALO II) and 1000-mg mefloquine group (MEF II). This difference between the earlier and later treatment groups is significant ($P<0.05$, ANOVA) and is attributed to active detection and earlier treatment of malaria cases in troops during the last 9 months of the study.

The number of previous malaria infections by history ranged from 0 to >10 in the HALO I group (median, 3). The majority of patients in the other three treatment groups previously had ⩽3 malaria infections, with a median of 1 in HALO II, and 2 in MEF I and MEF II groups. Patients in all the treatment study groups acquired their malaria infection from similar locations along the south-eastern Thai-Kampuchean border.

On admission, 25–45% of the patients had measurable serum sulfa levels (this method detected sulfones); less than 10% had any detectable quinine levels. There was no significant difference between the groups in serum quinine or serum sulfa levels. Thai marines routinely take one tablet of Maloprim (a combination of dapsone and pyrimethamine) weekly for prophylaxis of malaria. This would explain the high percentage of patients with positive serum assays for sulfa. All patients with any history of drug ingestion were observed for 48 hours prior to treatment to ensure that their malaria was not resolving because of the earlier administration of antimalarials.

Efficacy of halofantrine for falciparum malaria

The first 20 patients treated with halofantrine received an initial dose of 1000 mg followed by 500 mg 6 hours later. Recrudescence of malaria occurred in 7 of these patients, the cure rate being 65% (13/20). The remaining 62 patients treated with halofantrine were given 500 mg every 6 hours for 3 doses. Recrudescence occurred in 7 of these patients, the cure rate being 88% (53/60). All treatment failures on the triple-dose (HALO II) regimen were at the RI level. Six of the failures occurred between days 21 and 28 post-treatment and one on day 14. One treatment failure on the double-dose (HALO I) regimen was at the RII level. The other 6 treatment failures were at the RI level. The times of recrudescence were similar to the HALO II regimen with 5 recrudescences between days 21 and 28 post-treatment and one on day 12. Two recrudescent patients, CH 107 and CH 112, were retreated with 1000 mg mefloquine because of a history of tetracycline allergy and both were cured. All other failures were successfully treated with a 7-day course of quinine plus tetracycline.

The mean parasite clearance time for the HALO I regimen was 83.5 ± 23 hours (mean ± 1 standard deviation) and for the HALO II regimen 76 ± 19 hours. This was comparable to the mean parasite clearance time of 75.4 ± 25.2 hours for patients treated with 1000 mg of mefloquine and 78.8 ± 28.8 hours for patients treated with 1500 mg of mefloquine.

The mean fever clearance time (mean ± 1 standard deviation) for the HALO I regimen was 60.1 ± 34.8 hours and for the HALO II regimen 59.6 ± 38.1 hours. The fever clearance times in the mefloquine treated patients were 52.1 ± 30.3 hours and 55.8 ± 33.5 hours in the high- and low-dose groups, respectively. There was no significant difference between the four groups for parasite or fever clearance times.

The mean initial parasite counts for patients in the four treatment groups varied between 20 000 and 45 000 per mm^3. There was no significant difference in reported symptoms among the groups despite significantly different mean initial parasite counts. When both halofantrine groups and both mefloquine groups are combined there was no significant difference in initial parasite count between the halofantrine and mefloquine groups.

In vitro assays of parasite sensitivity to halofantrine in the 7 recrudescent patients treated with the HALO I regimen revealed a mean 50% inhibitory dose (ID_{50}) of 1 ng/ml, with 95% confidence limits of 0.3 and 1.7 ng/ml (Table 1). This was not significantly different from the mean ID_{50} value of a random sample of 33 isolates obtained along the Thai-Kampuchean border. The mean ID_{50} value for this latter group of isolates was 0.68 ng/ml, with 95% confidence limits of 0.5 and 0.8 ng/ml.

In vitro parasite sensitivity in the HALO II group to halofantrine in 5 of the 7 recrudescent patients revealed a mean ID_{50} value of 1.79 ng/ml, with 95% confidence limits of 1.11 and 2.88 ng/ml (Table 1). This significantly greater mean value is due to two patients with a high ID_{50} suggestive of resistant parasites. Parasite sensitivity to halofantrine was not determined in the remaining two cases in which recrudescence occurred on the HALO II regimen.

Serum levels of halofantrine and a primary metabolite, *N*-desbutyl halofantrine, were measured in 14 patients who developed recrudescent malaria and in 63 patients who were cured by treatment. Day-3 serum levels of the total drug (parent compound plus active metabolite) and the active metabolite alone were both significantly higher (Student's *t*-test) in the cured patients than in the treatment failure group ($P<0.001$ and $P<0.05$, respectively). No difference was detected in serum levels of halofantrine between the HALO I and HALO II treatment failures (Table 2). The recrudescent patients' mean day-3 serum level of halofantrine was approximately half that of

Table 1. Data on 14 recrudescent cases in the halofantrine treatment groups

Patient number	Clearance time (h)		Initial parasite count (per mm³)	Gastrointestinal intolerance	Recrudescence/ post-treatment day	Halofantrine level[a] on day 3 (ng/ml)	Drug dose (mg/kg)	ID_{50} (ng/ml) on the day of recrudescence	
	Parasite	Fever							
HALO I group:									
CH 14	89 5	168	73 372	None	RI/27	166.4	28.8	MEF HALO	7 20 3.30
CH 15	77	56	63 163	None	RI/14	53 5	25.0	MEF HALO	2.93 0.61
CH 18	—	—	93 213	Diarrhoea	RII/7	32 3	25.0	MEF HALO	15.05 1.11
CH 20	132	19	24 700	None	RI/21	179.3	27.7	MEF HALO	9 32 0.95
CH 24	72	56	98 023	None	RI/21	173.8	25.0	MEF HALO	32.79 4.25
CH 34	84	28	47 040	Diarrhoea	RI/21	149.0	28.8	MEF HALO	19.17 1.71
CH 36	78	44	26 620	None	RI/27	157.9	27.8	MEF HALO	3.95 0.32
HALO II group:									
CH 57	94	140	27 639	None	RI/12	47.2	25.9	MEF HALO	— —
CH 98	144	207	12 920	None	RI/21	92.4	27.3	MEF HALO	14.40 1.60
CH 107	70	144	8 120	Vomiting in first 48 h	RI/21	74.2	27.8	MEF HALO	1.60 0.80
CH 112	70	45	6 980	None	RI/21	62.2	25.4	MEF HALO	8.51 4 18
CH 126	67	68	31 540	None	RI/26	82.1	28.3	MEF HALO	— —
CH 128	96	68	4 440	None	RI/28	601.5	31.9	MEF HALO	— 7.99
CH 144	88	76	33 200	Vomiting and diarrhoea	RI/21	100.1	32 3	MEF HALO	3.02 0.43

[a] Level of parent drug plus metabolite in serum

Table 2. Halofantrine serum levels on day 3 among cured patients and treatment failures

	Mean serum level (ng/ml)	
	Treatment cures	Treatment failures
Total drug:[a]		
Both groups ($P<0.001$): (63 cures, 14 failures)	229 (190.5, 275.4)[b]	104.7 (69.2, 158.5)[b]
HALO I: (12 cures, 7 failures)	218.8 (178.6, 267.9)	112.2 (70.2, 179.5)
HALO II: (51 cures, 7 failures)	245.5 (198, 304.8)	84.5 (43.1, 166.0)
Metabolite only:		
Both groups ($P<0.05$): (63 cures, 14 failures)	131.8 (95.5, 182)	61.7 (38.9, 97.7)

[a] Parent drug plus metabolite.
[b] Figures in parentheses are the 95% confidence limits.

the cured patients. The results indicate widely scattered halofantrine serum levels and large inter-individual variation.

Efficacy of halofantrine against P. vivax

In 7 of the 62 patients on the HALO II treatment regimen, the erythrocytic forms of *P. vivax* were noted on blood smears between day 14 and day 28 post-treatment. Two patients were treated with a course of chloroquine for vivax during the study, one at day 14 and one at day 21; these patients were excluded from the efficacy calculations. One of the 65 patients treated with mefloquine developed *P. vivax* parasitaemia 28 days after treatment; none of these patients had recrudescent *P. falciparum* malaria. Halofantrine has no exo-erythrocytic activity and, given its functional half-life of 5.5 days in plasma, the 2 to 4 weeks' post-dosing drug levels would not be expected to be adequate for suppression of *P. vivax* blood forms.

Efficacy of mefloquine for falciparum malaria

Mefloquine (WR 142,490), as the hydrochloride salt, was chosen as the most effective drug with which to compare the performance of halofantrine. The first 40 subjects, randomized to receive mefloquine, were treated with a single oral dose of 1500 mg (MEF I regimen); this dose level was curative in 97% of patients (38/39).

In an attempt to minimize side-effects, the remaining 25 patients, who were to receive mefloquine, were treated with a single oral dose of 1000 mg (MEF II regimen) (*10*). This dose was curative in 88% of patients (22/24). There was no statistically different difference in cure rates between the high- and low-dose mefloquine regimens.

One patient treated with the high-dose MEF I regimen had an RII response to the drug. Culture of this patient's parasites at the time of drug failure and subsequent determination of its sensitivity to mefloquine revealed a high ID_{50} value, indicating that drug failure was most likely due to parasite resistance (Table 3). This conclusion was strengthened by the finding of adequate mefloquine blood levels in this case. Three patients treated with the MEF II regimen had RI responses with recrudescence of infection on days 21, 28, and 32 post-treatment (Table 3). In one of these cases the 50% inhibitory dose to mefloquine *in vitro* was significantly increased. No mefloquine blood levels were available on these patients.

Drug tolerance and toxicity

Post-dosing symptoms were seen in all four treatment groups. A side-effect was defined as a symptom appearing only after drug administration. Such symptoms were more common with mefloquine treatment but the difference in frequency of each reported symptom between the halofantrine and mefloquine groups was not statistically significant. Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, and abdominal pain occurred in 15% to 25% of patients in both the HALO I and HALO II groups. Patients in the high-dose mefloquine group had more nausea (30% vs. 16%) and diarrhoea (48% vs. 40%) than those in the low-dose mefloquine group. Vomi-

Table 3. Data on four recrudescent cases in the mefloquine treatment groups

Patient number	Clearance time (h)		Initial parasite count (per mm³)	Gastrointestinal intolerance	Recrudescence/ post-treatment day	Drug dose (mg/kg)	ID_{50} (ng/ml) on the day of recrudescence
	Parasite	Fever					
MEF I group:							
CH 12	—	56	70 799	Epigastric pain	RII	30.30	MEF 16 56 HALO 1.70
MEF II group:							
CH 109	110	72	87 664	Diarrhoea	RI/28	20.83	MEF 6.27 HALO 1.55
CH 150	53	24	5 760	Diarrhoea in first 48 h	RI/21	19.23	MEF 13.77 HALO —
CH 145	71	No fever	11 160	Diarrhoea and abdominal pain	RI/23	20.83	MEF 2.13 HALO —

ting and abdominal pain were documented in 10–25% of patients receiving mefloquine. Asymptomatic subjects constituted 40% of the halofantrine group and 25% of the mefloquine group.

Isolated symptoms or physical findings occurred in a small number of patients treated with the HALO II regimen and the MEF II regimen. In the HALO II group, one subject experienced neuromuscular spasms, another had jaundice, a third showed mouth ulcers, and a fourth had premature ventricular contractions. In subjects administered the MEF II regimen, one experienced arthralgia, another had jaundice, a third showed acute haemolysis, and a fourth had premature ventricular contractions.

The halofantrine patient with neuromuscular spasms had received a phenothiazine anti-emetic 48 hours previously. The halofantrine patient with mouth ulcers had no other skin or mucous membrane lesions. Both patients with premature ventricular contractions had a previous history of this abnormality, and both resolved within 48 hours without treatment.

Laboratory parameters

There was no significant overall rise in liver enzymes or blood urea nitrogen following drug treatment in any group (paired *t*-test). There was a consistent fall in haematocrit in all drug groups at day 7 post-treatment, which was probably secondary to the haemolysis seen in acute malaria infections (paired *t*-test, $P<0.05$). Platelet counts in all groups improved markedly post-treatment ($P<0.001$).

On examination of individual patient records for signs of post-treatment hepatic toxicity, a rise above the normal range in SGOT, SGPT, bilirubin or alkaline phosphatase was seen in 5–10% of study patients at day 7 after drug therapy. It should be noted that these laboratory abnormalities could be attributed to an active malaria infection and may not be indicative of drug toxicity. These changes were not correlated with any particular treatment group.

DISCUSSION

This clinical field trial shows that halofantrine was a highly efficacious antimalarial for the treatment of falciparum malaria in an area endemic for multidrug resistance. It cured 88% of the patients who received three doses of 500 mg at 6-hour intervals, which compares favourably with mefloquine. The rapid parasite and fever clearance times were also comparable with those seen with mefloquine.

The low circulating levels of halofantrine and *N*-desbutyl halofantrine among the recrudescent patients suggests poor absorption as the etiology of drug failure with this halofantrine formulation. In addition, only 4 of the 14 patients whose infections recrudesced following halofantrine treatment had *in vitro* evidence of parasite resistance.

Although the HALO I regimen was effective in phase II clinical studies in non-immune volunteers in the USA, these volunteers had been inoculated with a cryopreserved *P. falciparum* Vietnam Smith strain, and were treated very early in the course of their illness when parasitaemia was low.

With both halofantrine regimens used in this study,

there was wide individual variation in drug absorption and the clinical failures exhibited much lower day-3 drug levels in the serum. It should be noted that both the total drug dose administered and the mean total drug level in serum at day 3 were not higher in the 3-dose group than in the 2-dose halofantrine group, but the cure rate was dramatically improved. Thus, it became evident that two important factors in determining antimalarial drug efficacy were not measured in this study: the peak drug level and the area under the drug concentration–time curve (i.e., the total amount of drug absorbed). Pharmacokinetic studies are required so that a new dosing schedule that would maximize absorption can be designed because even the most recently produced formulations (a tablet and a syrup) showed no advantage in bioavailability over the capsule formulation used in this study (M. J. Shmuklarsky, unpublished data). The poor solubility of the drug at a higher pH probably limits the absorptive area to the upper duodenum, and rapid transit times in ill patients would severely limit the amount of drug absorbed.

Although the issue of cross-resistance was not addressed in this study, the two halofantrine failures were cured with mefloquine. One of them had an *in vitro* drug sensitivity pattern suggestive of halofantrine resistance; however, both these patients had low halofantrine levels at day 3, and hence could have failed because of an inadequate drug level.

In conclusion, halofantrine hydrochloride is a new alternative drug for the treatment of falciparum malaria in areas of increasing drug resistance. Further use of this new antimalarial is awaiting the development of a new dosing schedule spanning 24–36 hours that would ensure better absorption and adequate blood levels of the drug in every infected patient.

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RÉSUMÉ

PALUDISME: EFFICACITÉ THÉRAPEUTIQUE DE L'HALOFANTRINE (WR 171,669) LORS DES PREMIERS ESSAIS PRATIQUES EFFECTUÉS EN THAILANDE

Dans cet essai clinique, on a administré de l'halofantrine à 82 soldats thaïlandais semi-immuns, en poste le long de la frontière séparant la Thaïlande du Kampuchea et infestés par *Plasmodium falciparum*; il s'agissait d'une étude randomisée en double aveugle destinée à évaluer l'efficacité thérapeutique de ce produit vis-à-vis de l'infestation acquise naturellement en Asie. Les sujets étudiés avaient entre 21 et 50 ans, présentaient des numérations parasitaires allant de 500 à 100 000 par mm^3 et ne montraient aucune complication grave du paludisme, telle que vomissements prolongés et atteinte du système nerveux central. Ils ont été hospitalisés dans une région non impaludée pendant 21 jours à la suite du traitement. Tous ceux qui présentaient une recrudescence de la maladie ont été traités pendant 7 jours par le sulfate de quinine à raison de 650 mg toutes les 8 heures et par le chlorhydrate de tétracycline à raison de 500 mg toutes les 8 heures, et sont de nouveau restés en observation pendant 21 jours à la suite de ce second traitement.

L'halofantrine a été donnée sous forme de gélules contenant 250 mg de chlorhydrate. Les 20 premiers malades ont été traités par une dose de 1000 mg, suivie 6 heures après d'une dose de 500 mg (groupe HALO I) et les 62 malades restants ont été traités par 3 doses de 500 mg administrées à 6 heures d'intervalle (groupe HALO II). Le groupe témoin a reçu du chlorhydrate de méfloquine en comprimés de 250 mg; 40 sujets témoins ont reçu 1500 mg de méfloquine en une dose orale unique (groupe MEF I) et les 25 sujets restants ont reçu une dose unique de 1000 mg (groupe MEF II).

Les quatre groupes traités (HALO I, HALO II, MEF I et MEF II) présentaient tous au moment de l'admission dans l'étude des paramètres comparables: poids, âge, transaminase glutamique oxalo-acétique (SGOT), transaminase glutamique pyruvique (SGPT), bilirubine totale, phosphatase alcaline, azote uréique du sang, hématocrite et numération parasitaire.

Dans le groupe HALO I, le taux de guérison était de 65% (13/20). L'efficacité a été meilleure avec le groupe HALO II soit 88% (53/60). Tous les échecs thérapeutiques du groupe HALO II étaient dus à une résistance de degré RI. Six de ces sept échecs se sont manifestés entre le 21^e et le 28^e

jour après le traitement. Les échecs thérapeutiques du groupe HALO I étaient dus dans un cas à une résistance RII et dans six cas à une résistance RI; cinq des six échecs RI se sont manifestés entre le 21e et le 28e jour.

Les parasites ont disparu en moyenne au bout de 75 à 84 heures dans les quatre groupes. La fièvre a disparu en moyenne au bout de 52 à 60 heures, également dans tous les groupes. On n'a observé aucune différence significative entre les groupes pour ces deux phénomènes.

Les concentrations sériques de médicament total (halofantrine plus son métabolite actif, la N-desbutyl halofantrine) ont été analysées chez 14 sujets ayant présenté une recrudescence et chez 63 sujets guéris. Les concentrations sériques de médicament total et de métabolite actif seul étaient significativement plus élevées au 3e jour chez les sujets guéris que chez les autres ($P < 0{,}001$ et $P < 0{,}05$ respectivement). Au 3e jour, la concentration sérique en médicament total des sujets présentant une recrudescence était environ la moitié de celle des sujets guéris.

On a identifié *P. vivax* chez 7 malades du groupe HALO II sur 62, entre le 14e et le 28e jour après le traitement. Ces infestations étaient exo-érythrocytaires au moment de l'admission dans l'étude. Sur les 65 sujets traités à la méfloquine, un seul a montré une infestation à *P. vivax* au 28e jour.

Des symptômes gastro-intestinaux tels que nausées, vomissements, diarrhée et douleurs abdominales sont apparus chez 15 à 25% des sujets des groupes HALO I et HALO II. Le groupe MEF I a présenté plus de nausées que le groupe MEF II (30% contre 16%) et l'on a signalé des épisodes de diarrhée chez 48% des sujets du groupe MEF I et 40% des sujets du groupe MEF II. Dix à 25% des sujets des groupes MEF I et II ont présenté des vomissements et des douleurs abdominales. Quarante-deux pour cent des sujets des groupes halofantrine n'ont présenté aucun symptôme, contre 25% pour les groupes méfloquine.

Aucune de ces différences concernant les symptômes post-médication entre les groupes HALO et MEF n'était statistiquement significative.

En conclusion, l'halofantrine s'est révélée un antipaludique très efficace dans une région d'endémie à *P. falciparum* polypharmacorésistant. Les faibles concentrations circulantes d'halofantrine trouvées chez les malades ayant présenté une recrudescence laissent à penser qu'une mauvaise absorption a été à l'origine de l'échec thérapeutique. Sur les 14 sujets ayant présenté une recrudescence après traitement par l'halofantrine, seuls 4 ont fait la preuve *in vitro* d'une résistance parasitaire.

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