

## Halofantrine versus quinine-Fansidar combination in the treatment of post-chloroquine falciparum parasitaemia

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### SUMMARY

The standard first-line treatment for malaria in adults in Papua New Guinea is chloroquine; for severe and treatment-failure malaria standard therapy is a combination of quinine and Fansidar (sulphadoxine-pyrimethamine). These standard treatments are currently under revision. The present study evaluated the effect of halofantrine in treatment-failure falciparum malaria in adults in Port Moresby compared to standard therapy. In the halofantrine group all parasites were cleared by day 5 after starting therapy, in the quinine-Fansidar group by day 7. There was no evidence of recurrence of parasitaemia during the 21-day follow-up in either group. Nausea was associated with halofantrine use in 68% of patients. In the quinine-Fansidar group 79% had muffled deafness, 32% tinnitus and 26% dizziness; 32% of patients withdrew from treatment on day 2 because of intolerance to quinine. Halofantrine in this study population provided an efficacy against treatment-failure falciparum malaria similar to that of quinine-Fansidar, with a more favourable profile of adverse effects.

### Introduction

The existence in Papua New Guinea (PNG) of *Plasmodium falciparum* strains resistant to chloroquine was first reported in 1976 (1). Since then, the spread of these strains has been gradual from northwest towards southeast culminating in widespread chloroquine resistance with increasing frequency in many parts of the country (2). Resistance to amodiaquine and sulphadoxine-pyrimethamine (Fansidar) is also well documented (3,4). The level of resistance to Fansidar is low and no reports of complete clinical failure to quinine or quinine-Fansidar combination have been documented.

There is a general consensus, at present, that quinine and Fansidar can still be relied upon for providing clinical cure. The drugs remain effective and are the drugs of choice in severe and multidrug-resistant malaria. Unfortunately, quinine has inherently been associated with cinchonism, characterized by tinnitus, muffled hearing, dizziness and vertigo at normal therapeutic concentrations. For

many patients cinchonism is not well tolerated and this frequently leads to poor compliance with the standard dose regimen. The efficacy of quinine must be protected and one strategy is to alternate quinine with another antimalarial drug such as halofantrine.

Halofantrine is a highly effective drug against chloroquine-resistant *P. falciparum* malaria (5). Several studies have been conducted with this drug among Melanesian populations in the region (6,7) The results of these studies indicate good efficacy and acceptability making it a suitable candidate against chloroquine-resistant or multidrug-resistant falciparum malaria. A preliminary study was conducted to assess clinical efficacy, acceptability and compliance using standard dose regimens of halofantrine and quinine-Fansidar combination in patients who failed to respond to standard chloroquine treatment.

### Subjects and Methods

The study was conducted at the Port

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Moresby General Hospital (PMGH), Papua New Guinea, where *P. falciparum* malaria is predominantly endemic. Patients, males and females, attending the outpatient clinic from September 1996 to February 1998 were selected for enrolment into the study. These patients were semi-immune adults who were long-term residents of Port Moresby city. All had received chloroquine alone before enrolment and the major criterion for inclusion was that of persistent *P. falciparum* parasitaemia after day 5 of a standard chloroquine regimen (25 mg/kg over 3 days). Exclusion criteria included *P. falciparum* parasitaemia of  $\geq 10,000$  asexual forms/ $\mu\text{l}$ , lactation and a history of cardiovascular diseases or drug allergy, particularly to sulfonamides. Patients were given a full physical examination on initial presentation at enrolment and follow-up physical examinations were performed if indicated. For logistic reasons electrocardiography was not performed.

Patients were randomly assigned to receive the standard 1-day halofantrine regimen (500 mg every 6 hours - 3 doses) (halofantrine group) or 3-day quinine regimen (10 mg/kg every 8 hours for 3 days) plus Fansidar (3 tablets statim) (quinine-Fansidar group), using a random numbers table. In the quinine-Fansidar group patients received Fansidar half an hour before the start of quinine. The first doses of quinine and Fansidar and halofantrine were taken under supervision with water (about 100 ml) and the repeat doses, supplied in a pre-packed format, were taken at home after a meal. Compliance was defined by patients having completed the prescribed drug dosage regimen, which was monitored with tablet counts on follow-up days. Each patient was monitored at the outpatient malaria clinic from enrolment to the completion of the study and any adverse events emerging during treatment were noted.

Antimalarial efficacy was evaluated by the parasitaemia response. Peripheral thick films for examination for asexual forms of *P. falciparum* were taken on days 1 (start of medication), 2, 3, 5, 7, 14 and 21. Blood films were stained with phosphate-buffered Giemsa (10%, pH 7.4) and parasites (asexual forms) were counted against white cell count.

Treatment was considered curative for *P. falciparum* if parasites were cleared from blood films within 7 days after the start of treatment and remained so during the 21-day follow-up. Parasites failing to clear by day 7 were considered resistant to the treatment modalities. For the purpose of assessing the two-treatment outcome, analysis by intention to treat was performed, and p values of  $<0.05$  were considered statistically significant.

Each patient gave informed consent to participate in the study after its aims and purposes were explained. Approval for the study was obtained from the Medical Faculty Research Committee, University of Papua New Guinea.

## Results

38 patients meeting the selection criteria were enrolled for the study. These patients were randomized such that 19 received halofantrine and 19 the quinine-Fansidar combination. The baseline clinical characteristics and the parasitaemia level of the two treatment groups were comparable (Table 1).

Of the 38 patients, 9 (24%) did not complete the study. 3 of these patients were lost to follow-up on day 1, 2 in the halofantrine group and 1 in the quinine-Fansidar group, while 6 patients in the quinine-Fansidar group changed medication on day 2 because of quinine intolerance. Thus a total of 29 patients completed the follow-up, 17 patients (11 males and 6 females) in the halofantrine group and 12 (9 males and 3 females) in the quinine-Fansidar group.

In both treatment groups, parasites were cleared within 7 days of starting treatment. In the halofantrine group, 37% (7/19) of patients were cleared of parasites on day 3 of starting the treatment while the remainder became aparasitaemic on day 5. In the quinine-Fansidar group, 11% (2/19) of the patients were cleared of parasites on day 3, 32% (6/19) on day 5 and 21% (4/19) on day 7. There was no evidence of recurrence of parasitaemia during the 21-day follow-up in either group.

Adverse events for the two treatment groups are presented in Table 2. Nausea was the most

**TABLE 1**

CLINICAL CHARACTERISTICS OF MALARIA-INFECTED PATIENTS ON ADMISSION AND FOLLOW-UP

	Treatment group	
	Halofantrine	Quinine-Fansidar
<b>Admission</b>		
Number	19	19
Sex (M/F)	11/8	13/6
Mean age, years (range)	34 (18-55)	36 (19-45)
Weight, kg, range	45-75	44-80
Axillary temperature, °C, range	36.0-37.5	36.5-37.5
Parasitaemia, per µl, mean ± sd	3854 ± 2060	3693 ± 2120
<b>Follow-up</b>		
Parasite clearance time	5 days	7 days
Withdrawals	11% (n=2)	37% (n=7)
Compliance/Acceptability	90%	63%

sd = standard deviation

**TABLE 2**

NUMBER (PERCENTAGE) OF PATIENTS WITH ADVERSE EVENTS AFTER TREATMENT

Symptom*	Treatment	
	Halofantrine	Quinine-Fansidar
Nausea	13 (68)	3 (16)
Vomiting > 1 hour	3 (16)	0 (0)
Vomiting < 1 hour	2 (11)	1 (5)
Diarrhoea	2 (11)	1 (5)
Abdominal pain	1 (5)	0 (0)
Dizziness	2 (11)	5 (26)
Tinnitus	0 (0)	6 (32)
Transient deafness	0 (0)	14 (79)
Feeling hungry	2 (11)	5 (26)

\*Includes only emergent events related to treatment which were reported during treatment days and had not been present before enrolment into study groups

common adverse event reported (68%) in the halofantrine group, while other adverse events were minor. In the quinine-Fansidar group, muffled deafness accounted for 79% of the adverse events reported followed by tinnitus (32%) and dizziness (26%). Unexpectedly, a feeling of hunger was a frequent complaint

among patients (26%) in the quinine-Fansidar group. These patients had apparently taken quinine doses on an empty stomach on each occasion. No serious adverse events were reported in either treatment group.

6 patients (32%) withdrew on day 2 in the quinine-Fansidar group because of quinine

intolerance. Except for the 2 patients lost to follow-up, all patients completed halofantrine treatment and the drug was well tolerated. There was no clinical evidence of bradycardia or arrhythmia in any of the patients receiving halofantrine.

### Discussion

The efficacy of halofantrine and quinine-Fansidar combination in clearing post-chloroquine parasitaemia in this small study was comparable. In all the patients halofantrine cleared falciparum parasitaemia by day 5 and the quinine-Fansidar combination by day 7. Halofantrine and quinine are both schizontocidal agents but their speed of antimalarial action differs. This may partially explain the difference in parasite clearance times between the two treatment groups, in addition to the possible effect of residual chloroquine in the blood of some patients. While both drug treatments were equally effective within the limits of this study, halofantrine performed better than the quinine-Fansidar combination in terms of acceptability and compliance.

Despite the well-known antimalarial benefits of quinine pharmacotherapy, the treatment of a proportion of patients with the drug remains suboptimal. In this study one-third of the patients who were assigned the regimen containing quinine discontinued or failed to complete the treatment simply because they were unable to tolerate the adverse effects attributed to the quinine. These findings may have some important practical implications, such as poor compliance for outpatient medical practice where treatments are not supervised. Poor compliance with drug treatment is likely to produce poor therapeutic outcomes and encourages the emergence of drug resistance.

The results of this study, conducted in an area where quinine and Fansidar remain relatively effective against chloroquine-resistant *P. falciparum*, do not suggest that the combination of quinine-Fansidar should be replaced by halofantrine. They do, however, suggest that halofantrine treatment offers

similar efficacy with a more favourable adverse-effect profile than the quinine-Fansidar combination. Therefore halofantrine seems an alternative choice specifically against chloroquine-resistant falciparum malaria. However, since the study has dealt with only a small sample population in one geographical location, further studies are needed to explore the benefits of different drug treatments against treatment-failure malaria in Papua New Guinea.

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