EFFICACY AND SAFETY OF HALOFANTRINE IN PAKISTANI CHILDREN AND ADULTS WITH MALARIA CAUSED BY *P. FALCIPARUM* AND *P. VIVAX*

M Zafarullah Khan[1], Zeenat Isani[2], Tahir Masood Ahmed[3], Awn Bin Zafar[4], Nizamuddin Gilal[5], Sajid Maqbool[6], Khalid Mehmood[7], Iffaft Yazdani[8] and Karthik B Srinivasa[9]

[1]Mayo Hospital, Lahore; [2] National Institute of Child Health (NICH), Karachi; [3]Mayo Pediatrics Hospital, Lahore; [4]Murshid Hospital, Karachi; [5]Civil Hospital, Mirpurkhas; [6]Children Hospital, Lahore; [7]Civil Hospital, Karachi; [8]GlaxoSmithKline, Pakistan; [9]GlaxoSmithKline, India

Abstract. One hundred two patients aged 2-43 years diagnosed with acute malaria due to *P. falciparum* or *P. vivax* were treated with 3 doses of halofantrine (500 mg for ≥18 year old patients and 8 mg/kg of patient body weight for 2-17 year olds), with each dose administered once in 6 hours and followed up for 28 days. Out of 102 patients 63 had *P. falciparum*, 36 had *P. vivax* and 3 had unidentified species. Following three dose therapy, 96.1% (98/102) of patients were cured, 0.98% (1/102) showed improvement from baseline, 1.96% (2/102) did not respond and were considered as treatment failures and one patient had indeterminate data. The lone patient, who relapsed after 120 hours post dose 1, was cured following re-treatment on day 7. The median parasite clearance and fever clearance times, from the first dose, were 26 hours and 30 hours, respectively. Eleven point eight percent (12/102) of patients reported adverse events, of which abdominal pain, reported by one subject, was considered to be probably related to the drug and required corrective therapy. There were no serious adverse events or fatalities and none of the patients had a change in QT_c interval greater than 10%. Thirteen point seven percent (14/102) of patients had abnormal clinical laboratory parameters that normalized later.

INTRODUCTION

Globally, the incidence of malaria varies from 300-500 million clinical cases per year, of whom 1 to 2 million die due to malaria (World Health Organization, 1996). Malaria is prevalent in Africa, Asia and Latin America. In Pakistan malaria is endemic at low to moderate levels, with 82,526 cases reported in the year 2000 (Anonymous, 2005).

In Pakistan, resistance to chloroquine is on the rise, reported in 16-62% of infections with *P. falciparum*. Four to 25% of cases infected with *P. falciparum* have also been reported to be resistant to sulfadoxine-pyrimethamine and several cases of delayed parasite clearance have been observed in patients with *P. falciparum* infection treated with quinine.

A fixed-dose triple combination of mefloquine-sulfadoxine-pyrimethamine is used in Pakistan. As with others combinations, the rationale for this formulation is to prevent the development of drug-resistant parasites. Unfortunately, resistance to each of the three drug components has been reported.

In Pakistan, malaria poses a major health problem. Being a tropical country, Pakistan has a vast irrigational system encompassing many pools of stagnant water, especially following heavy rainfall. These factors provide ideal breeding grounds for mosquitoes. Transmission continues throughout the year but becomes more intense after the rains from July

Correspondence: Dr Iffaft Yazdani, GlaxoSmithKline Pakistan Ltd, 35 Dockyard Road, West Whasf, Karachi 74000, Pakistan.
E-mail: iffaft.k.Yazadani@gsk.com

to November (Burney, 1981). In Pakistan, falciparum malaria is more common in Sindh, Baluchistan and Punjab, and there has been a rapid rise the number or cases of in falciparum malaria among children in Karachi (Rafi, 1994).

In the past, the bark of cinchona tree and extracts of the wormwood plant were used to treat malaria, but the development of chloroquine as an antimalarial revolutionized malaria treatment. Chloroquine resistance has led to the need to develop other drugs (Wernsdorfer, 1994; Bloland, 2001). Halofantrine is a phenanthrenemethanol antimalarial agent used in the treatment of chloroquine-resistant and sulphonamide-pyrimethamine-resistant *P. falciparum* (Bryson and Goa, 1992; Karbwang and Na Bangchang, 1994). Halofantrine had been reported to be cardiotoxic and induce prolongation of the QT interval (Batey *et al*, 1997; Karle, 1997; Wesche, 2000; Lightbown *et al*, 2001).

In this study conducted in Pakistan, the efficacy and safety of halofantrine was evaluated in children and adults having uncomplicated malarial infection caused by *P. falciparum* and/or *P. vivax*.

PATIENTS AND METHODS

This was an open, non-comparative study conducted on hospitalized adult and pediatric subjects suffering from acute malaria infection due to either *P. falciparum* or *P. vivax*. All patients in this study were hospitalized for the first three days of the study, starting from the first day of administration of the drug and continuing until the end of third day. The patients were followed up on days 7, 14, 21 and 28. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and approved by the Ethics Committees of each center. The study was conducted from July to November 2003 at 7 centers in Pakistan: the National Institute of Child Health (NICH), Karachi; Civil Hospital Karachi; Mayo Hospital, Lahore; Children's Hospital, Lahore; Mayo Paeds, Lahore; Murshid Hospital, Karachi; and Civil Hospital, Mirpurkhas.

A total of 102 male and female patients over age 2 years, suffering from acute falciparum or vivax malaria were recruited after written informed consent was obtained from the patient or parent/guardian in the case of minors. A diagnosis of malaria was made on blood smears containing 1,000-200,000 parasites/mm^3. Other inclusion criteria were normal hematological and biochemical tests and the ability to take oral medication.

An electrocardiogram (ECG) was performed on all patients prior to entry into the study and 18 hours post-treatment. The corrected QT interval (QTc) was calculated manually for each ECG. The exclusion criteria were patients with signs of severe malaria, protracted vomiting, greatly decreased urine output, severe hypotension, central nervous system symptoms, children less than 2 years of age and under 10 kg, patients on diuretics or arrythmogenic drugs, those with cardiac disorders, a prolonged QT_c interval, significant concomitant disease or in whom oral therapy was not possible. Patients on other antimalarials were also excluded. Females of childbearing potential were required to use effective contraceptives.

After physical examination, blood samples were drawn for hematological and biochemical analysis. Adult patients were given 500 mg halofantrine (2 tablets of 250 mg each) every 6 hours for 3 doses (1,500 mg). Children were given halofantrine 8 mg/kg body weight. The drug was not given on a full stomach and fatty food was avoided for 24 hours after taking the medication.

Clinical assessment was done on days 0, 3, 7, 14 and 21, and included physical examination, evaluation of symptoms and any side effects. Axillary temperature was recorded twice daily for the first 4 days. If fever per-

sisted beyond 4 days, the temperature was measured until it normalized (36.5ºC) and was checked for an additional 24 hours. Thick and thin blood smears were examined for parasite counts twice daily for the first three days, or until smears were negative for at least 24 hours. Further smears were obtained and counts performed on days 7, 14 and 21 if positive for parasites beyond the first three days. Patients with persistently positive blood smears, or positive blood smears followed by negative blood smears on days 7, 14 or 21 were followed for an additional 14 days.

Hemoglobin, WBC, platelets counts, liver function tests (serum glutamate-oxaloacetic aminotranferase (SGOT)/ serum glutamate-pyruvate aminotransferase (SGPT), alkaline phosphatase (AP)), blood urea nitrogen (BUN) and creatinine were performed on days 0 and 7.

Statistical methods

All analyses were done on patients with data available (intention-to-treat cohort). Baseline signs and symptoms, prior and concomitant medication, and past and current medical conditions were summarized. Vital signs (systolic BP, diastolic BP, pulse, weight and temperature) were summarized. Efficacy analysis included determination of cure rate, relapse rate, parasite clearance time and fever clearance time. Cure rate was defined as the number of subjects who became symptom free and whose smears were parasite free and remained so for 21 days. Relapse rate was defined as the number of subjects whose blood smears initially become parasite free but then became positive again and required therapy. Parasite clearance time was defined as time (hours) required for blood smears to become parasite free, from the time of administration of the first dose. Fever clearance was the time (hours) taken for fever to return to normal, from the time of administration of the first dose. For safety analysis, the number of deaths and serious adverse events were summarized. The percentage of patients with adverse events was computed. The percentage change in the QT_c interval from baseline until 18 hours after the first dose was tabulated. The percentage of patients with clinically significant laboratory parameters was summarized.

RESULTS

There were a total of 102 patients, 63 with *P. falciparum*, 36 with *P. vivax* and 3 with unidentified species. Of the subjects (60.8% males and 39.2% females) enrolled in the study, 93 completed the study and 9 dropped out prior to day 28. These 9 subjects dropped out because they were cured prior to day 28. None of the drop-outs were due to serious adverse events. The mean age of the patients was 15.7 years (Table 1).

At least one baseline symptom was present in 56.8% of the patients. Fever was the most common symptom (72.6%) for which concomitant medication was administered. The mean systolic BP was 106 mmHg and

Table 1
Demographic characteristics.

Characteristics	Parameters or Categories	N = 102	
		Value or n	%
Age (Years)	Mean	15.7	-
	SD	9.9	-
	Median	12.6	-
	Minimum	2.2	-
	Maximum	43.8	-
Gender	Female	40	39.2
	Male	62	60.8
Race	Sindhi	45	44.1
	Punjabi	35	34.3
	Baluch	17	16.7
	Pathan	3	2.9
	Others	2	1.9

N = total number of patients; n (%) = number (percentage) of patients in a given category
Value = value of the considered parameter; SD = standard deviation

the mean diastolic BP was 67 mmHg. On day 3, the mean systolic BP was 107 mmHg and the mean diastolic BP was 69 mmHg. The mean pulse rate on entry was 106 beats per minute (BPM) which had dropped to 87 BPM by day 21. The mean temperature upon presentation (morning) was 37.7ºC which decreased to 36.2ºC by day 3.

Ninety-nine percent (101/102) of patients received all three doses of the drug and one patient missed the third dose.

The efficacy (cure rate) of the drug was 96.9% (98/ 102). 0.98% (1/102) showed improvement from baseline, 1.96% (2/102) did not respond and were considered as treatment failures and one patient had indeterminate data. The lone patient who relapsed 120 hours after the first dose was successfully re-treated on day 7. From the time of administration of the first dose, it took about 26 hours (median value) for the parasites to clear, and 93% of patients showed parasite clearance within the first 48 hours (Fig 1). Fever was present in 101 patients and defervesced by 30 hours of therapy (Fig 2). Fever re-appeared in 12 patients, but returned to normal within 4 days of the first dose (Table 2). One patient did not have fever at any time during the study.

Twelve patients reported at least one side effect/adverse event (AE) during the study. The majority (69%) of the side effects were mild. One patient complained of abdominal pain which was probably related to the drug. The symptom received after adjusting the dose of the drug. No serious side effects or fatalities were reported.

On ECG, 28 patients had no QT_c interval changes. Fifty-four patients had a QT_c interval between 0-1%, 6 patients between 1-2%, 2 patients between 2-10% and none above 10%.

In 14 cases abnormal clinical laboratory parameters (anemia, raised SGOT/SGPT, hyperbilirubinemia, lymphocytosis, lymphocytopenia, leukopenia, thrombocytopenia) were seen from days 0 to 7. These tests returned to normal by the end of the study.

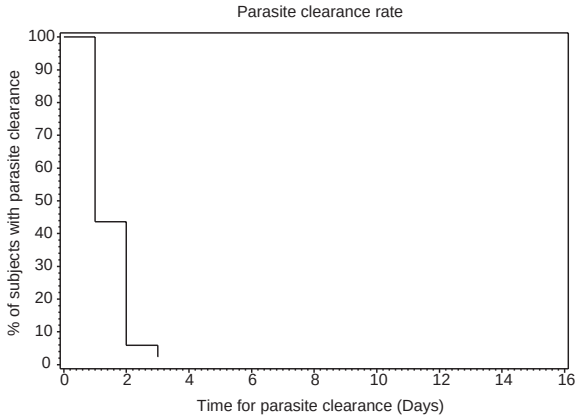

Fig 1–Time to parasite clearance during the study.

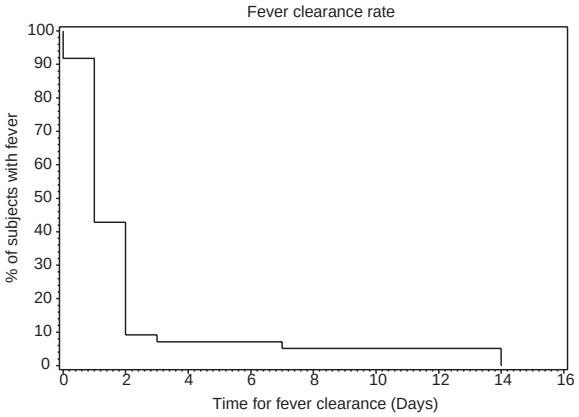

Fig 2–Time for fever clearance during the study.

DISCUSSION

Studies have shown the failure of chloroquine against *P. falciparum* and *P. vivax* (Sumawinata *et al*, 2003), creating the need for a more effective antimalarial. Chloroquine resistance was first reported in Latin America in 1959 and later in Thailand in 1962 (Harinasuta *et al*, 1962). Resistance had been reported in Kenya (Anabwani *et al*, 1996). In Pakistan, chloroquine resistance in falciparum malaria was first reported in Quetta in 1982

Table 2
Parasite and fever clearance time from the time of first dose.

	n	Median (hours)	Minimum (hours)	Maximum (hours)
Parasite clearance				
Without relapse	97	26	11	67
With relapse	1	327	-	-
Fever clearance				
Without fever re-appearance	85	30.0	4	161
With fever re-appearance	12	107.5	23	359
Overall	97	32.0	4	359

n = number of patients who got cure at the end of the study/ number of patients with fever clearance
Median = Median time for parasite clearance/ fever clearance (in hours)
Minimum/Maximum = Minimum/ Maximum time for parasite clearance/ fever clearance during the study

(Anwar and Zaheeruddin, 1984), then later in Punjab and the North Western Frontier Province (NWFP) (Khaliq *et al*, 1985; Nasreen, 1987; Humayun and Ali, 1991).

Increasing resistance to chloroquine and sulphadoxime-pyrimethamine has led to increased use of alternative antimalarials, including halofantrine, which has been widely used in Pakistan for more than a decade.

The present study was done to determine the efficacy and safety of halofantrine hydrochloride in the treatment of uncomplicated falciparum malaria in adults and children in Pakistan.

Over 96% of cases were cured with halofantrine. One patient had a relapse and required re-treatment on day 7; this patient recovered by day 14. The efficacy rate in this study is comparable to another study conducted by Salahuddin *et al* in 1997. Fever cleared in 30 hours in this study, which is earlier than the 36 hours reported in a previous study. The median parasite clearance time in this study was 26 hours, compared to 39.9 hours in a previous study. Adverse side effects were reported in 11.8% of subjects and laboratory abnormalities were reported in 13.7% of subjects. There were no serious side effects or fatalities.

Halofantrine is associated with prolongation of the QT_c interval and many studies have been carried out to assess its effect on the heart (Sowunmi *et al*, 2000; Touze *et al*, 2002). These studies indicate a dose dependent effect. In the present study, the change in QT_c interval was below the clinical limit of 10% (John, 2003).

The present study shows that the resistance pattern of halofantrine has not changed since 1997 (Salahuddin *et al*, 1997). The drug has a high efficacy rate with fever improving earlier than that in previous studies. Halofantrine is a safe and effective treatment for uncomplicated *P. falciparum* and *P. vivax* in the Pakistani population.

ACKNOWLEDGEMENTS

National Institute of Child Health (NICH), Karachi; Civil Hospital, Karachi; Mayo Hospital, Lahore; Children's Hospital, Lahore; Mayo Paeds, Lahore; Murshid Hospital, Karachi and Civil Hospital, Mirpurkhas received research grants from GlaxoSmithKline Pharmaceuticals Pakistan. Dr Iffat Yazdani and Karthik Srinivasa are employees of GlaxoSmithKline.

In accordance with the requirements of the International Committee of Medical Journal Editors, Prof M Zafarullah Khan, Prof Zeenat Isani, Prof Tahir Masood Ahmed, Dr Awn Bin Zafar, Dr Nizamuddin Gilal, Prof Sajid Maqbool and Prof Khalid Mehmood had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

Anabwani GM, Estamai FO, Menya DA. A randomized controlled trial to assess the relative efficacy of chloroquine, amodiaquine, halofantrine and fansidar in the treatment of uncomplicated malaria in children. *East Afr Med J* 1996; 73: 155-8.

Anwar M, Zaheeruddin. Falciparum malaria – emergence of resistant strain in Pakistan. *Pak Arm Forces Med J* 1984; 3: 1-6.

Anonymous. [Cited 2005 Mar 15]. Available from: URL: http://www.emro.who.int/rbm/Epidemiology-current.htm

Batey AJ, Lightbown ID, Lambert PJ, Edwards G, Coker SJ. Comparison of the acute cardiotoxicity of the antimalarial drug Halofantrine *in vitro* and *in vivo* in anaesthetized guinea-pigs. *Br J Pharmacol* 1997; 122: 563-9.

Bloland BP. Drug resistance in malaria. Geneva: WHO, 2001; 4: 1-27.

Bryson HM, Goa KL. Halofantrine. A review of its antimalarial activity, pharmacokinetic properties and therapeutic potential. *Drugs* 1992; 43: 236-58.

Burney MI. The unfinished battle. *Pak J Med Res* 1981; 20: 27-30.

Harinasuta J, Migasina S, Boonnag D. Chloroquine resistance in falciparum malaria in Thailand, Singapore: UNESCO First symposium on scientific knowledge on tropical disease. 1962.

Humayun M, Ali G. Distruibution of antimalarial parasite in NWFP. *J Med Sci* 1991; 1: 111.

John RH. The ECG in practice. 4th ed. Churchill Livingstone, 2003: 98.

Karbwang J, Na Bangchang K. Clinical pharmacokinetics of halofantrine. *Clin Pharmacokinet* 1994; 27: 104-19.

Karle JM. X-ray crystal structure of the antimalarial agent (-)-Halofantrine hydrochloride supports stereospecificity for cardiotoxicity. *Antimicrob Agents Chemother* 1997; 41: 791-4.

Khaliq AA, Sarwar M, Fox E, Strickland GT. Chloroquine resistant *Plasmodium falciparum* in Punjab. *Pak J Med Res* 1985; 24: 89-93.

Lightbown ID, Lambert PJ, Edwards G, Coker SJ. Potentiation if halofantrine-induced QT_c prolongation by mefloquine: correlation with blood concentrations of halofantrine. *Br J Pharmacol* 2001; 132: 197-204.

Nasreen T. Sensitivity of *Plasmodium* to chloroquine, amodiaquine and fansidar in Gujranwala district. *Pak J Med Res* 1987; 26: 186-91.

Rafi S, Memon RA, Rao MH, Billo AG. A change of plasmodium species infecting children in Karachi over the last decade. *J Pak Med Assoc* 1994; 44: 162-4.

Salahuddin N, Ahmad S, Haider T, Rana T. Efficacy and safety of halofantrine hydrochloride in the treatment of acute malaria. *Infect Dis J Pakistan* 1997; Oct-Dec: 11-12.

Sowunmi A, Falade CO, Adedeji AA, *et al*. Patterns of change in the electrocardiogram after halofantrine treatment of acute uncomplicated falciparum malaria in children. *Clin Drug Invest*. 2000; 20: 229-35.

Sumawinata IW, Bernadeta, Leksana B, *et al*. Very high risk of therapeutic failure with chloroquine for uncomplicated *Plasmodium falciparum* and *P vivax* malaria in Indonesia Papua. *Am J Trop Med Hyg* 2003; 68:416-20.

Touze JE, Heno P, Fourcade L, *et al*. The effects of antimalarial drugs on ventricular repolarization. *Am J Trop Med Hyg* 2002; 76: 54-60.

Wernsdorfer WH. Epidemiology of drug resistance in malaria. *Acta Trop* 1994; 56: 143-56.

Wesche DL, Scguster BG, Wang WX, Woosley RL. Mechanism of cardiotoxicity of halofantrine. *Clin Pharmacol Ther* 2000; 67: 521-9.

World Health Organization. World malaria situation in 1993, part I. *Wkly Epidemiol Rec* 1996; 17-24.