Principles of Internal Medicine, vol 2,12th edn. Eds Wilson JD, Braunwald E, Isselbacher KJ, *et al.* Humberg, McGraw Hill Book Company, 1991, p 1875.

2. O'Brien WM, Ladu BN, Bunim JJ. Biochemical, pathological and clinical aspects of alkaptonuria: Review of world literature from 1584 to 1962. Am J Med 1971, 25: 253-258.
3. Choudhary HR, Gokhroo RK, Arora SK, Bhardwaj B, Bhati RS, MathurMS. Report of two cases of alkaptonuria. J Assoc Phys India 1983, 31: 676-677.
4. Desai HJ, Mehta HC, Undevia SV, Thakore HR, Shah RM. Alkaptonuria with diabetes mellitus—A case report. Indian J Med Science 1978, 32: 77-79.
5. Ghai OP. Essential Pediatrics, 2nd edn. New Delhi, Interprint, 1990, p 393.

Efficacy of Halofantrine in Malaria

H.G. Bilolikar
A.C. Bagade
MA Phadke
P.S. Gambhir

Malaria continues to be a major health problem in the tropical countries. In India, about 2 million suffer from the disease every year; the reported cases in 1989 being 20,17,823 with 268 deaths and in 1990, 17,77,263 cases and 222 deaths(l). Thirty five per cent of the total cases of malaria in our country occur in children below 15 years of age(2). Of late, more and more cases appear to be resistant to chloroquine and also to other antimalarials(3). This is particularly so with *Plasmodium falciparum* malaria(4). In India, chloroquine resistant strains of *P. falciparum* were demonstrated in 19 states of the country in 1986(5). Halofantrine, a phenanthrene-methanol, is an orally administered schizonticidal drug, effective against both chloroquine sensitive and resistant strains of *Plasmodia.* We report our results with 46 children suffering from malaria treated with halofantrine using a 3 dose regimen of 8 mg/kg 6 hourly(6,7).

From the Department of Pediatrics, B.J. Medical College and Sassoon General Hospitals, Pune 411 001.

Reprint requests: Dr (Mrs) M.A. Phadke, Professor and Head of the Department of Pediatrics, BJ. Medical College, Pune 411 001.

Received for publication: September 23, 1992; Accepted: February 23, 1994

Material and Methods

Forty six children suffering from malaria caused by *Plasmodium vivax* and/or *Plasmodium falciparum* or *Plasmodium ovale* were included. The children attended the Outpatient Department or were admitted to the Pediatric ward of Sassoon General Hospitals, Pune. The criteria used for selection were history of fever and the presence of malarial parasite on peripheral smear (gametocytes or asexual forms).

Children who had received antimalarials in the past 14 days and had become afebrile were excluded. Children with complicated malaria and who were critically ill were also excluded.

A complete history and physical examination was obtained at admission and regularly during the followup of 4 weeks. Blood smear parasite count was done daily during the first week and later weekly. Hematocrit and white blood cell count (total and differential) were done on admission and then on days 1, 3, 7 and 14 and at the time of discharge from the hospital. Urine analysis for albumin, sugar and bile pigments, and blood levels of urea and creatinine were also done on the same days. Adverse effects of the drug if any, were noted.

Informed parental consent was obtained and all patients entering the trial were treated with halofantrine hydrochloride oral suspension, 8 mg/kg body weight 6 hourly for 3 doses. The patients were considered as cured if parasites cleared from the blood and there was no recrudescence during the 4 weeks follow up. If parasitemia occurred during follow up, another course of halofantrine was given. The fever clearance time was defined as the time from the drug administration till the temperature became normal and remained so for atleast 48 hours. The parasite clearance time was the time from the drug administration till there was no parasitemia.

Results

The patients ranged in age from 6 months to 12 years (mean 7 years + 2.9 years); 22 were boys. Fever, headache and rigors were the most frequent presenting symptoms *(Table I*). Splenomegaly was observed in 24 (52.2%) patients before the initiation of therapy, while anemia (hemoglobin < llg/dl) was present in 16 (34.9%) patients. Splenomegaly and anemia persisted in 6 (13%) and 10 (21.7%) cases, respectively after 28 days of therapy. Headache was present in 36 (78.3%) patients which subsided within 4 days after treatment in all cases. Rigors or chills were observed in 31 (67.4%) patients and in majority of the patients these disappeared within 7 days of the treatment.

Twenty seven patients (58.7%) were infected with *P. vivax* and 17 patients (37%) were infected with *P. falciparum.* Two patients had mixed infection (one had *P. vivax* and *P. falciparum,* whereas the other had *P. vivax and P. ovale).* Twenty six patients (56.5%) became parasite free within

TABLE I–*Response to Halofantrine in Malaria*

Presenting features	Day 0		Day 2		Day 3		Day 4		Day 7		Day 14		Day 28	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Fever	46	100.0	24	52.1	14	30.4	4	8.7	2	4.3	1	2.2	-	-
Headache	36	78.3	14	30.4	2	4.3	-	-	-	-	-	-	-	-
Rigors/chills	31	67.4	18	39.1	18	39.1	6	13.0	4	8.7	1	2.2	-	-
Splenomegaly	24	52.1	24	52.1	24	52.1	20	43.4	16	34.8	8	17.4	6	13.0
Anemia	16	34.8	14	30.4	14	30.4	14	30.4	14	30.4	12	26.0	10	21.7

72 hours of the therapy, whereas 42 patients (91.3%) were parasite free within 4 days of therapy *(Fig. 1).* All except one patient were parasite free within the first 7 days of therapy. The mean (SD) parasite clearance time was 56 (53.3) hours. The mean (SD) fever clearance time was 51 (41.3) hours. One patient continued to have fever and parasitemia at the end of 2 weeks of the therapy and was administered a second dose. This patient became afebrile and parasite free 5 days after the second dose and remained parasite free at the end of 28 days.

The drug was palatable and was free of any significant side effects. Three patients had vomiting after the first dose, however, they tolerated the drug on repeat dose. Nausea was reported in additional 4 patients. No significant changes in any of the laboratory parameters were reported.

Discussion

Halofantrine hydrochloride, introduced for the treatment of malaria is found to be effective against sensitive as well as multi-drug resistant strains of *P. falciparum* and *P. vivax* by different workers(8,9,10).

Clinical trials have confirmed its efficacy in the treatment of falciparum and vivax malaria in Pakistan, Kenya, Solomon Islands, Gabon and other parts of Africa. The reported cure rate from these studies is 96-100%(ll-14).

In the previous studies, the parasite clearance time averages 36 to 72 hours and the fever clearance time averages 24 to 60 hours(3,7,12,13), which compares favorably with our results. The mean parasite clearance time in this study was 56 hours and the mean fever clearance time was 51 hours. In Kenya and Solomon Islands the mean parasite clearance time was 65.4 hours and 41.5 hours, respectively (3,13).

No serious drug related toxicity has been reported by other workers(ll-14). We observed nausea in 6.4% and vomiting in 8.7%

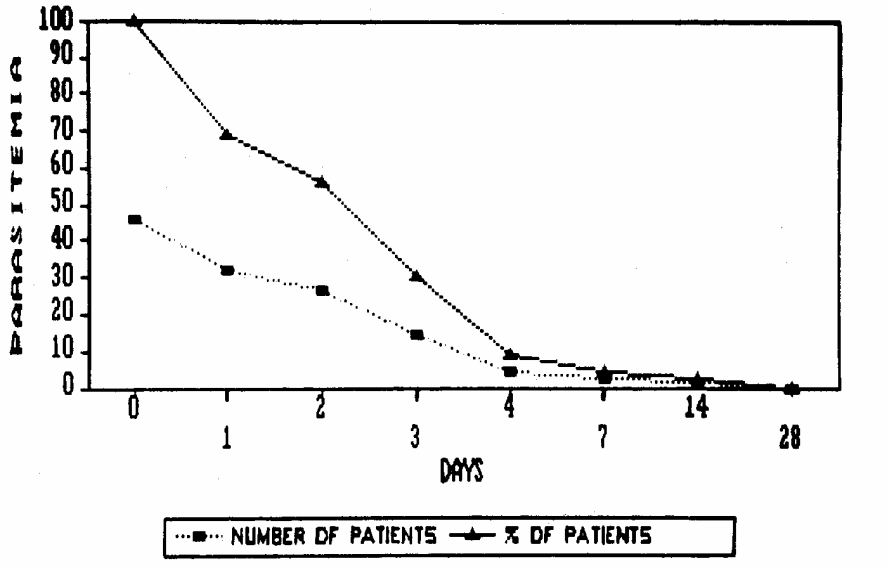

Fig. 1. Decrease in parasitemia following halofantrine therapy.

patients. Earlier studies have indicated minor gastrointestinal symptoms and pruritus as the common side effects. Pruritus was not observed in the present study. Hematological and biochemical parameters in our study indicated no adverse influence of the drug and all earlier studies have reported similar experience(3,8,9,12,14).

Halofantrine, one of class of the amino-alcohols, the phenanthrenemethanols, was first identified as a potential antimalarial by Wiselogle during World War II. It was rediscovered as an antimalarial useful in chloroquine resistant cases in the 1960s by the Walter Reed Army Institute of Research(7).

The drug halofantrine hydrochloride, is administered orally in three doses of 8 mg/kg in children and 500 mg in adults, 6 hours apart(6,7). It is available as a 2% suspension or as 250 mg tablets of halofantrine hydrochloride. The drug is palatable, unlike most antimalarials. Since the drug can at present, only be given by mouth, its use is restricted to the treatment of mild and moderate disease. The cost of halofantrine is similar to mefloquine in other countries, it is not yet commercially available in India.

In this trial, one of the most significant features that was noted was the ease of administration and acceptance by the patient. This could be attributed to the better palatability, the single day of treatment and the relative lack of side effects. Coupled with this was the rapid recovery from illness.

This was a pilot study, and there is a need to study further the clinical efficacy of halofantrine, to compare it with existing antimalarial drugs in a randomized double blind trial, and to study its pharmacokinetics in Indian subjects.

Acknowledgement

The authors are thankful to M/s. Eskayef, Bangalore for the supply of halofantrine hydrochloride (Halfan) suspension for this study.

REFERENCES

1. Vishwakarama GK, Wadhwa VS, Bhasin VP. Positive cases of malaria in India. *In:* Health Information of India, 1991. Central Bureau of Health Intelligence, Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India, New Delhi, 1991, p 137.
2. Kondrashin AV, Rashid KM. Situation in India: Age related malaria. *In:* Epidemiological Considerations for Planning Malaria Control in South East Asia region. WHO Regional Publication, South East Asia Series, 1987, 17: 280.
3. Wirima J, Molyneux ME, Khoromana C, Gilles HM. Clinical trials with halofantrine hydrochloride in Malawi. Lancet 1983, 2: 250-252.
4. Rieckmann KH, Sax LJ, Campbell GH, Mrema JE. Drug sensitivity of *Plasmodium fakiparum in vitro* technique. Lancet 1972, 1: 22-23.
5. Kondrashin AV, Rashid KM. Situation in India: Malaria and drug resistance. *In:* Epidemiological Considerations for Planning Malaria Control in South East Asia Region. WHO Regional Publication, South East Asia Series, 1987, 17: 355.
6. WHO Practical Chemotherapy of Malaria. WHO Technical Report Series, 1990, p 805.
7. Leading Article: Halofantrine in the treatment of malaria. Lancet 1989,2: 537-538.

8. Cosgriff TM, Boudreaux EF, Pamplin CL, Doberstyn EB. Evaluation of antimalarial activity of the phenanthrenemethanol halofantrine: WR 17 1669. Am J Trop Med Hyg 1982, 31: 1075-1079.

9. Canfield CJ, MacDonald BS, Neuman DA, Shaw JA. Treatment of falciparum malaria from Vietnam with phenanthrene-methanol: WR 33063 and a quinolene methanol: WR 30090. Antimalarial Agents Chemotherapy 1973, 3: 224-227.

10. Couland JP, LeBras J, Matheron S, Rossignol JFR. Treatment of imported cases of falciparum malaria in France with halo fantrine. Trans R Soc Trop Med Hyg 1986, 80: 615-616.

11. Watkins WM, Oloo AJ, Mjomba M, Koech DK, Gilles HM. Chloroquine resistant falciparum malaria: Responsiveness to treatment with halofantrine. Parasitology Today 1989, 1: 46-52.

12. Rab SM, Sheikhani MS, Mahmoud SA, Jaffary SJH. The efficacy of halofantrine hydrochloride in acute malaria. A study of 74 patients from Karachi, Pakistan. Parasitology Today 1989, 1: 37-44.

13. Parkinson D, Balmer V, Korinohowa A, Kere N. The effectiveness of halofantrine for the treatment of acute malaria in adults in the Solomon Islands. Parasitology Today 1989, 1: 27-35.

14. Salako LA, Sowunmi A, Walker O. Evaluation of the clinical efficacy and safety of halofantrine in falciparum malaria in Ibadan, Nigeria. Trans R Soc Trop Med Hyg 1990, 84: 644-647.

Aerococcus Viridans Endocarditis

T. Augustine
Thirunavukkarasu
B. Vishnu Bhat
B.D. Bhatia

Aerococcus viridans is an infrequent human pathogen. Bacterial endocarditis caused by this Gram positive coccus is extremely rare and hence this case report.

Case Report

A ten-year-old boy was admitted with complaints of fever of one month, dyspnea and fleeting arthralgia of 7 days as well as hematuria of one day duration. The fever was high grade intermittent without any chills and rigors. General physical examination revealed a pale child with heart rate of 140/min, temperature of l02°F, blood pressure of 100/70 mm Hg in the left upper

From the Department of Pediatrics, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry 605 006.

Reprint requests; Dr B.D. Bhatia, Professor and Head, Department of Pediatrics, JIPMER, Pondicherry 605 006.

Received for publication: March 22, 1993; Accepted: July 21, 1993