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Halofantrine in the treatment of uncomplicated falciparum malaria with a three-dose regimen in Papua New Guinea: a preliminary report

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SUMMARY

We evaluated the efficacy and safety of halofantrine in 19 patients with acute uncomplicated falciparum malaria. Each patient received oral halofantrine hydrochloride 500 mg every 6 hours for 3 doses (total 1.5 g). In almost all the patients clinical symptoms of malaria and parasitaemia disappeared within 2 and 3 days, respectively, of starting treatment. We observed no recurrence of parasitaemia during 14 days of follow-up. Tolerance to halofantrine was good except for minor and self-limiting gastrointestinal side-effects. Haematological and biochemical indices were not seriously affected. Halofantrine-induced prolongation of Q-T/Q-Tc intervals was the consistent cardiac manifestation in 84% of patients. The Q-T/Q-Tc interval prolongation increased with each dose; it reached a maximum between 18 and 24 hours and thereafter returned to baseline. These preliminary data indicate that, apart from the cardiac side-effects, halofantrine is an effective and safe drug, well tolerated by most of the patients in the study.

Introduction

The emergence and rapid spread of *Plasmodium falciparum* strains resistant to treatment with 4-aminoquinolines and other antimalarial drugs have posed a major public health problem for Papua New Guinea (PNG) (1-3). In view of these developments the introduction of alternative drugs to chloroquine, and possibly quinine, may become necessary in the near future and would necessitate clinical trials of these new alternatives. Halofantrine hydrochloride, a phenanthrenemethanol derivative, is a newer antimalarial drug. It is one of many separate chemical entities examined for antimalarial activity under the drug development program of the Walter Reed Army Institute of Research (WRAIR), Washington, DC, USA (4). The drug is now commercially available in some parts of the world and is being marketed under the trade name Halfan by Smith Kline & Beecham (UK). To date, some million courses of halofantrine have been administered worldwide for curative purposes in areas of chloroquine resistance (5).

Clinical studies of halofantrine in different countries using the currently recommended 3-dose regimen of 500 mg every 6 hours have shown high cure rates against *P. falciparum* malaria (6-12) in areas of multidrug resistance. The standard 3-dose regimen appears to be relatively safe. Frequently reported side-effects include nausea, vomiting, abdominal pain, diarrhoea, severe headache and dizziness. Pruritus is an unusual phenomenon and has so far been observed only among patients of African origin receiving halofantrine (9,13-15), the majority of whom were chloroquine itchers (16). Halofantrine use has occasionally been associated with loss of taste, body weakness, insomnia, intravascular haemolysis and morbilliform rash (9,17,18). However, the most serious unwanted effect of halofantrine is on the heart, characterized by delayed

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atrioventricular conduction and prolonged ventricular repolarization, causing prolongation of the Q-T/Q-Tc interval. These halofantrine-induced cardiac changes have been well documented (5,19-24).

Among the Melanesian ethnic populations of the South Pacific, only two studies have been conducted, one in Solomon Islands (25) and the other in Papua New Guinea (26). The objective of the latter study was to assess the prophylactic potential of halofantrine rather than clinical efficacy. The aim of the present study was to evaluate clinical efficacy and safety using a 14-day in vivo test with the standard 3-dose regimen in uncomplicated falciparum malaria. We report here the preliminary results, which we hope will form the baseline data for future study.

Subjects and Methods

The study was conducted at the malaria outpatient clinic of Tabubil Hospital, Western Province of Papua New Guinea. This is a base hospital for the mining population and their dependants (total population of 2500) and the local inhabitants of the surrounding villages and hamlets. The township is situated on a plateau, 1700 feet above sea level. The annual rainfall is high and local malaria transmission is low or, until recently, non-existent. The subjects studied were mineworkers and their dependants returning from different coastal regions of the country after variable periods of recreational leave, usually 3-7 days. The study was conducted from July 1994 to March 1995.

The study was approved by the Medical Faculty Research Committee, University of Papua New Guinea, the Medical Research Advisory Committee of PNG and the Chief Medical Officer, Tabubil Hospital. All the subjects received full explanation of the purpose and the procedures of the study, including likely adverse effects, before written consent was obtained from the patients or guardians.

Subject selection

Patients presenting themselves at the malaria outpatient clinic were recruited. Inclusion criteria included age 18 years and over, the presence of asexual forms of *Plasmodium falciparum* and no history of antimalarial drug ingestion within 3 weeks of presentation. Those patients with signs of cerebral malaria (convulsions, confusion, loss of consciousness), with evidence of severe malaria (deep jaundice, prostration, a high parasitaemia of 90,000/µl or greater), pregnant or lactating, on drug therapy for other diseases, or with a history suggestive of heart disease including hypertension were excluded from enrolment. The main exit criteria from the study were clinical cure or adverse events which in the opinion of the attending physician were causally related to halofantrine. In cases where there was failure to improve as judged by (a) persistent or episodic temperature 37.5° C for more than 72 hours after admission or (b) a parasitaemia 48 hours after the start of treatment still 50% of that recorded on admission, halofantrine was stopped and alternative treatment instituted with either chloroquine or quinine.

Clinical and laboratory procedures

Patients were admitted into the hospital before drug administration. Each patient was interviewed and was given a complete physical examination, including baseline measurements such as pulse rate, blood pressure and respiratory rate, before drug administration. Biochemical indices (urea, creatinine, hepatic function, random blood sugar levels) and haematological values (haemoglobin, ESR, white cell count and platelet count) were determined on days 0 (admission), 1, 7 and 14.

A 12-lead electrocardiogram (ECG) tracing (1 mV/10 mm, paper speed of 25 mm/sec) was recorded on each patient before treatment, before each dose of halofantrine and on days 1, 7 and 14 post treatment. The ECG analysis was based on visual measurement of P-R interval, R-R interval, the QRS complex and the Q-T interval. The Q-T interval was measured from the start of the QRS complex (Q wave) to the point at which the T wave trace returns to the T-P baseline. Q-Tc (the calculated Q-T interval, adjusted for heart rate) was read using a standard ECG nomogram (the upper limit of the normal Q-Tc interval being 0.42 sec).

Drug administration and patient management

Halofantrine was given orally as the hydrochloride salt (Smith Kline & Beecham, UK). Each patient was given 500 mg (two 250 mg tablets) every 6 hours for 3 doses (1.5 g). Each dose of the drug was administered under clinical supervision with a glass of milk (100 ml) to improve drug absorption (complying with the company's regulation for a shorter hospital stay). After each dose the mouth was inspected to ensure that the tablets had been swallowed. There was no case of vomiting immediately after drug ingestion; thus no repeat dosing was required. Drug treatment was considered curative if there was clearance of *P. falciparum* parasitaemia within 5 days (based on the half-life of halofantrine) and no recrudescence during the 14-day follow-up. If parasitaemia occurred during the follow-up period halofantrine treatment was regarded as a failure and oral quinine (10 mg/kg 3 times daily) with a single dose of pyrimethamine/sulphadoxine combination (Fansidar) was given.

Each patient was questioned and examined for the presence and severity of adverse drug reactions daily during the period in the hospital and at every subsequent visit. Adverse events occurring immediately and during the study period were recorded on a standard adverse event data sheet. The times the adverse events appeared and disappeared including their intensity and duration were noted. Each patient received standard symptomatic care and normal hospital diet while in hospital.

Monitoring of parasitaemia and fever responses

Thick and thin blood films were made at times 0, 6 and 12 hours and on days 1, 2, 3, 5, 7 and 14. Parasite counts of asexual forms were made against a count of 1000 white cells and multiplied by 5, assuming a white cell count of 5000 per µl (27). Temperature was taken 6-hourly for the first 24 hours, then daily until discharge from hospital, and weekly thereafter, for two weeks. Fever, defined as axillary temperature of ≥37.5°C, and level of parasitaemia were monitored and recorded on standard data collection forms.

The parameters for assessing clinical efficacy of halofantrine were parasitaemia clearance time (PCT), fever clearance time (FCT), cure rate and recrudescence rate. PCT was defined as the number of hours between the first dose of medication and the first of two successive negative blood smears. The PCT_{50}= time taken for parasites to fall by 50% from the pretreatment value and PCT_{99}= time taken for parasites to fall by 99% from the pretreatment value. FCT was the interval between the first dose and the time at which the patient became and remained afebrile (<37.5°C); FCT_A=time taken for the temperature to fall for the first time below 37.5°C.

Results

Admission data

A total of 20 male adult patients were recruited into the study but 19 patients completed the follow-up and were evaluable. Their ages ranged from 18 to 45 years. They had a mean weight of 64 kg (range 44-80 kg). The presenting symptoms were headache (63%), fever (53%), gastrointestinal symptoms of nausea, vomiting and diarrhoea (42%), dizziness (21%), joint pains (16%), chills and rigors (11%) and cough (5%). Four patients (21%) had splenomegaly and one (5%) hepatosplenomegaly. The liver and spleen enlargement became nonpalpable within 14 days of treatment. None of the patients showed signs of anaemia.

Adverse events attributable to halofantrine treatment

Three patients developed adverse events which we thought were attributable to the drug treatment. Two had gastrointestinal symptoms of diarrhoea and vomiting an hour after the last dose of halofantrine; the symptoms resolved spontaneously. One of the two had jaundice on admission and hepatitis A and B were excluded on the basis of negative viral antibodies; the patient made an uneventful recovery.

The third patient had to be readmitted 4.5 hours after discharge from hospital. On readmission his pulse was weak, blood pressure was low (systole of <100 mm Hg; diastole not detected) and temperature was

high (40°C). Cerebral malaria was suspected and quinine infusion (in dextrose/saline) was instituted despite negative blood smears for malarial parasites. Follow-up blood smears for malarial parasites were still negative and intravenous quinine was changed to oral therapy. The patient made a remarkable recovery and was discharged 48 hours after readmission. Retrospective ECG analysis showed a prolonged QT/QTc interval of 12% from baseline, a phenomenon likely to result from the halofantrine treatment.

Efficacy assessment

Parasitaemia

The mean pretreatment parasitaemia level was 3605 (a range of 142 to 29,526) per µl and the mean PCT was 52 ± 20 hours (range 12 to 96 hours). The post-treatment decline of parasitaemia was variable initially. 42% (8/19) of patients showed an increase in parasitaemia 6 hours after the first dose of halofantrine but with subsequent doses the parasitaemia levels declined considerably. The overall profile of the parasite clearance over time is presented in Figure 1.

Fever

The mean FCT was 29 ±18 hours. However, the FCT may not truly represent the dynamics of fever since admission temperatures were variable. Only 10 (53%) of the patients presented with fever (temperature ≥37.5°C). The remaining 9 were afebrile on admission but 6 of these became febrile between 6 and 12 hours after treatment; 3 remained afebrile throughout the study period. Thus the FCT was not a useful measure of efficacy in this study.

Cure and recrudescence rates

By day 5 all patients were aparasitaemic (100% cure rate), which persisted on follow-up days until day 14. Though this does not exclude parasitaemia after day 14 none of the patients returned with malaria within two weeks of completing the study.

Laboratory data

Biochemistry

The serum electrolytes were within normal limits throughout the study period.

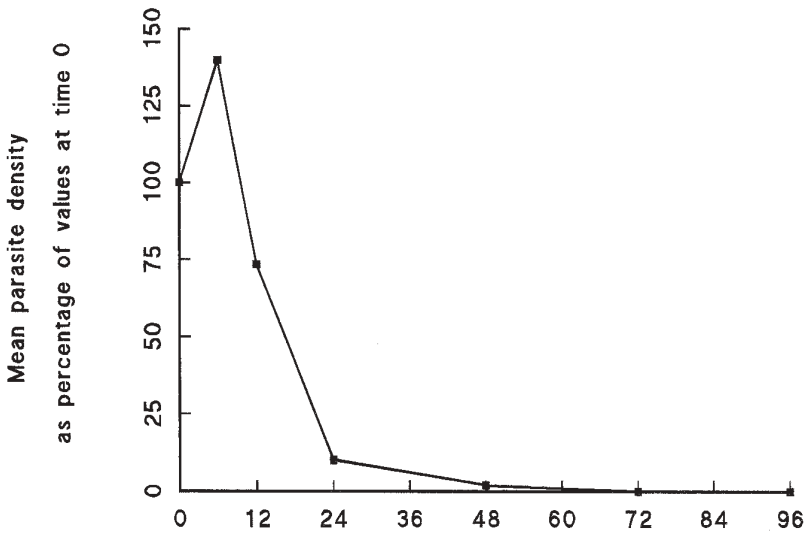

Figure 1. Fall over time (in hours) in mean asexual *P. falciparum* parasitaemia as a percentage of the pretreatment value in 19 patients treated with halofantrine.

Pretreatment total serum bilirubin and hepatic enzymes (AST and ALT) were elevated in some patients but in all these cases values returned to within the normal range by day 14. However, in addition, in 8 patients there was a post-treatment rise in ALT only between day 1 and day 7. By day 14 the ALT levels had returned to within normal values in all except 2 of these patients, in whom the return to normal took another 2 weeks.

Haematology

Except for a few minor pre- and post-treatment changes, haematological values were within normal ranges. Two patients had thrombocytopenia (platelet count below 100 x 10^9/l) on admission while three had values below 100 x 10^9/l on day 1 post treatment; all recovered uneventfully. One patient had neutropenia (white cell count < 4 x 10^9/l) on day 1 post treatment, but recovered on day 2. Anaemia was not a feature nor was there any evidence of intravascular haemolysis over the study period.

Electrocardiographic changes

The most consistent and persistent ECG changes were observed in the Q-T and Q-Tc intervals, which were prolonged in 16 (84%) of the patients. These changes were progressive with each dose of the drug and reached peak values between 18 and 24 hours post treatment. Thereafter, the intervals returned to values within the normal range by 48 hours. The heart rate and PT/RR intervals were not affected by the drug treatment except for QRS complex prolongation, which was observed in some patients between 8 and 12 hours post treatment.

Discussion

Our preliminary results indicate that halofantrine is effective and relatively safe using the standard 3-dose regimen. Parasitaemia was cleared within 72 hours in all except one, who became aparasitaemic 96 hours after treatment. The mean clearance times of parasitaemia and fever were 52 and 29 hours, respectively. These observations indicate that the local parasites were susceptible to the drug and that halofantrine was well absorbed in the study population.

The results have also not been seriously affected by the drug intolerance which was found in a few of our patients who received halofantrine. Vomiting after drug administration occurred in only 2 out of 19 patients and their clinical outcomes were uneventful. No evidence of serious haematological or biochemical toxicity was noted following treatment; though some elevation in AST and ALT was found in some individuals it was probably related more to the disease than to treatment (28-30). One patient, however, had to be readmitted a few hours after discharge because of adverse cardiovascular events. The cause remains unknown but post-treatment events linked to halofantrine cannot be excluded; fortunately, the patient made a rapid recovery.

While a post-treatment rise in parasitaemia from baseline may or may not predispose to treatment failure, the rise observed in our study was transient and seemed not to have affected the treatment outcome. We believe the transient rise in parasitaemia reflected the return of sequestered parasites to peripheral blood from central compartments. As parasites mature they attach to deep vascular endothelium, and simultaneous reentry of large numbers of progeny into the peripheral circulation following treatment may increase parasite counts. The reentrant parasites were susceptible to the drug since the level of parasitaemia did not continue to rise above its value at 48 hours or 60 hours post treatment. Nor were the counts higher at 36, 48 or 60 hours than they had been 12 hours earlier, which might have suggested treatment failure (31).

The cardiac toxicity of halofantrine, characterized by prolongation of the Q-Tc interval, is now well documented (5,19-24). In our study, 84% of the patients had Q-Tc interval prolongation from baseline. Although we did not measure the plasma levels of halofantrine, all these patients showed progression of Q-Tc intervals with each subsequent dose, implying dose-dependent Q-Tc interval lengthening. Our findings not only confirm previous reports but also provide data from a different ethnic and geographical background. Certain variations in the length of Q-Tc interval prolongation have been observed

in some studies (5) and these variations may be attributed to different definition and measurement criteria used in ECG assessment in different studies. However, it is important not to overlook individual variation in susceptibility to the halofantrine-induced cardiac effect that may exist in different human populations. The susceptibility of each human individual is unique, yet population-specific ECG patterns may help to define factors, such as dietary habit (32), likely to contribute to cardiac toxicity. And should such patterns confirm that different susceptibility factors exist in different human populations, the use of halofantrine will ultimately have to be tailored for particular geographical areas and human populations. These are important considerations since halofantrine has a novel antimalarial activity against chloroquine-resistant falciparum malaria; its usefulness should not be overshadowed by cardiac toxicity.

In order to improve the therapeutic profile of halofantrine, its prescription should follow certain guidelines, especially those included in the drug sheets provided by the manufacturer, and care must be exercised in its use. Importantly, clinicians should weigh a patient's risk, including history of cardiac disease and the availability of alternative therapy, before using halofantrine. Although pretreatment ECGs are poor predictors of Q-Tc lengthening during drug treatment, at least they provide a baseline guide and confidence in proceeding to halofantrine use. Pretreatment ECGs may also help to detect any unsuspected cardiac conditions or pretreatment Q-Tc interval prolongation, both of which may indicate the possibility of subsequent complication in susceptible individuals. However, such prerequisites for halofantrine use cannot be carried out in every situation, especially in rural settings where ECG equipment is not available.

There is now good evidence for the clinical and parasitological efficacy of halofantrine in cases of simple falciparum malaria. Clinical studies of halofantrine conducted in different endemic countries, using the currently recommended 3-dose regimen of 500 mg every 6 hours, have shown acceptable clinical and biological results (6-12). While our preliminary results confirm much of what has already been reported, a number of study design problems may limit the interpretation of our results. The time profile of parasitaemia clearance (PCT) in our study is consistent with some previous studies (8,22,25), and differs from others (8-10,33). Variations in study design, mode of drug administration and host immune status may partly contribute to such differences in results observed across the spectrum of different studies.

In conclusion, we acknowledge that while our results clearly confirm and extend earlier findings, the data are not sufficiently robust to warrant any recommendations about the drug. Our study has dealt with only one small geographical location and a small sample population. We believe that further studies are needed. Nevertheless, notwithstanding its cardiac toxicity, halofantrine is a novel antimalarial for drug-resistant falciparum malaria. The current 3-dose regimen was safe and practical for most of the patients in the present study.

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