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The Use of Halofantrine Hydrochloride in Acute Malaria

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SUMMARY

Malaria remains one of the commonest causes of fever in this part of the world. We studied the effectiveness of halofantrine hydrochloride in a total of 32 patients (males 17, females 15, mean age 30.25 years) with acute malaria. The main presenting features were high temperature (100%), headache (98%), rigors (96.9%) and all had positive slides for malarial parasites. All of the 32 patients responded to treatment, and became asymptomatic within 2-5 days of initiation of therapy. There was complete clearance of parasiteamia in all patients, and there was no evidence of alteration in renal, liver or hematological function secondary to therapy. These parameters were monitored before the initiation of therapy and on the 4th and 7th post therapy days. No side effects secondary to therapy were observed in these patients. In conclusion, halofantrine is a safe and effective drug for the treatment of acute malaria.

INTRODUCTION

Malaria is a worldwide malady, which continues to be difficult to control and eradicate even in this day and age. There were approximately 5.1 million cases of malaria worldwide in 1987, excluding countries south of the Sahara[1]. Pakistan also lies in the affected geographical belt. Initially thought to be an eradicable disease, it was observed that certain strains of the malarial parasite had over the years acquired resistance to conventional anti-malarial drugs[2]. It was this drug resistance that led to the search and development of different drugs to combat resistant malaria. Halofantrine is one of the latest drugs in use for this purpose. Concerns have been expressed over it's poor bio-availability and variable absorption in its present formulation and for this purpose a new formulation of this drug has been developed. The objective of this study was to investigate the safety and efficacy of this new formulation, against acute malarial infections.

PATIENTS AND METHODS

The study included a total of 32 patients of both sexes over 10 years of age, who presented with high temperature and were found to have positive blood smears for malarial parasites.

The patients included in the study had to fulfill the following inclusion criteria in order to qualify for the study:-

1. Patients willing to agree to the study and provide informed (written/oral) consent.
2. Blood smears containing at least 500 parasites per cu.mm. and not more than 250,000 parasites.
3. Presence of normal hematological and biochemical tests within the context of active critical malaria.

The following exclusion criteria was applied to exclude patients from the study:-

1. Severe malaria or severe accompanying disease; temperature over 40.5 ° C, protracted vomiting, greatly decreased urine output, severe hypotension or severe CNS symptoms.
2. Severe concomitant disease which makes the assessment of the therapeutic response difficult; for example, systemic bacterial infections, hepatic and/or renal insufficiencies or chronic disease associated with fever, severe malnutrition).
3. Patients where oral therapy is not possible because of effects of the basic disease.

4. Children under 10 years of age and patients under 26kg. of body weight.
5. Pregnancy

Patients fulfilling the aforementioned criteria underwent a physical examination and blood tests for heamatologic and biochemical analysis. Patients then received 1, 1.5, or 2 (125mg) tablets of the micronised halofantrine hydrochloride, in the form of white uncoated unscored tablets orally, 6 hourly for the next three doses. The dose received being determined by the patient's body weight:-

Body Weight	Dosage (x 3)
26 - 31 kg	125mg
32 - 40 kg	187.5mg
> 40 kg	250mg

Following dosing, the patients were followed up for a period of 28 days. The patients were encouraged to return for the follow-up visits on post therapy days 4, 7 and 28 in order to document recrudescence of parasitemia following initial clearance.

The follow-up assessment was based on the following parameters:-

1. Clinical
   a. Symptom review
   b. Adverse event review
   c. Physical examination
2. Parasitology
3. Haematology
4. Biochemistry

RESULTS

A total of 32 patients were treated with halofantrine at the Shaikh Zayed Hospital. Of these, 17 were males and 15 females with a mean age of 30.25 years and a mean weight of 49 kg. Twenty -one out of these patients were positive for Plasmodium Falciparum and the remaining 11 patients were smear positive for Plasmodium Vivax. Patient profile is described in Table 1.

Table 2 shows the frequency of different symptoms with which the patients presented at the time of admission, and on follow-up days 4 and 7. The commonest symptom at presentation was that of rigors with a frequency of 96.5%, followed by headache in 93.8% of the patients. Headache and itching were observed in only a single patient on the 4th post treatment day but these symptoms also disappeared on the 7th follow-up day. Thus at the end of seven days all of our patients were completely asymptomatic. Table 3, summarizes the temperature, pulse rate and blood pressure profile on days 1, 4 and 7, which all came to the baseline values on the 4th follow-up day.

Table 1: Patient profile.

Total No. of patients	32
Males:	17
Females:	15
Age Range:	14-60 years (Mean 30.25 years)
Weight Range:	43-78 kg (Mean 49 kg.)

Table 2: Relative frequency of symptoms.

Symptom	*Day 1*	*Day 4*	*Day 7*
Headache	30+ (93.8%)	1+ (3.1%)	Nil
Rigors	31+ (96.9%)	Nil	Nil
Fever	32+ (100%)	Nil	Nil
Itching	1+ (3.1%)	1+ (3.1%	Nil

Table 3: Clinical signs.

Sign	*Day*	*Min.*	*Max.*	*Mean*	*SD*
Temp.	1	99	104.5	102.85	1.47
	4	98.4	98.4	98.4	0
	7	98.4	98.4	98.4	0
Pulse	1	90	124	112.6	9.16
	4	82.50	72	90	8.23
	7	68	74	78	0.23
BP (Sys.)	1	110	160	124.88	13.02
	4	100	130	94	11.53
	7	105	110	104.32	0.79

The hematological data is shown in Table 4. All the patients in our group also had their liver

function tests (bilirubin, alkaline phosphatase, AST, ALT), renal profiles (urea, creatinine) and E. C. G.'s monitored at the time of presentation and on follow-up on days 4 and 7. All these parameters remained within normal limits.

Table 4: Hematological data.

Parameter	*Day*	*Min.*	*Max.*	*Mean*	*SD*
Hb	1	10.5	14.8	13.03	1.18
	4	9.2	14.6	13.08	1.18
	7	11.8	12.8	12.20	.53
TLC	1	4900	11600	8803.13	1934.66
	4	5500	11800	8337.93	1513.37
	7	6800	9500	8300	1374.77

DISCUSSION

Malaria continues to represent a major health problem in tropical countries in terms of geographical spread, high morbidity and mortality. According to estimates the population at risk being greater than 2 billion 3.

Malaria was thought to be an eradicable disease during the 50's and 60's, because of effectiveness of pesticides in killing mosquito vectors, and the introduction of chloroquine then a new anti-malarial drug. however inspite of an ambitious program of disease eradication, in the mid-seventies there was an alarming resurgence of the infection in places, particularly in South-East Asia, that had become partly or completely disease free[4]. Many factors have contributed to defeat earlier hopes of containing or abating the disease; thus poor socio-economic status of involved countries, precluding adequate government funding; faulty planning and management; qualitative and quantitative inadequacy of manpower; and the emergence and rapid spreading of resistance, both of vector mosquitoes to insecticides and of pathogenic plasmodia to anti-malarial drugs[5,6].

Resistance of human plasmodia to anti-malarial drugs has developed punctually with the extensive use of each product. The impact of this phenomenon was not very great as long as effective insecticides were extensively used to control the anopheles mosquito vector[7]; but starting in the early seventies, when the use of insecticides was drastically reduced because of technical and economic difficulties, resistant plasmodium strains have become more and more widespread both in places where they had been in existence for a long time and in places until recently unaffected[8].

Plasmodium resistance is particularly alarming in the case of chloroquine, the most active and widely used anti-malarial drug, and of the Falciparum strain, the most widespread and virulent pathogen of the malarial group[9-11]. Among other things it seems that chloroquine resistant strains, unlike antifolic resistant ones, enjoy a biological advantage over chloroquine susceptible strains in the sense of greater stability of that population, which persists also in the absence of drug pressure; this maybe one of the factors that have determined the rapid dissemination of resistance to 4-aminoquinolone drugs[12].

Drug resistance according to a WHO scientific committee defined plasmodium drug resistance "the ability of a parasite strain to survive and for to multiply despite the administration and absorption of a drug given in doses equal to or higher than the usually recommended but within the limits of tolerance to the subject"[13].

Knowledge acquired in regard to plasmodium resistance to drugs is derived largely from research conducted in experimental models hence applicable to human models only with due circumspection, we may recognize that the exact mechanism of plasmodium resistance is far from completely understood, and certainly not for all the available drugs, which is not surprising, as resistance is in many ways connected with the drugs own mechanism of action, and this is not always known in detail. In both cases the development of resistant strains reflects a spontaneous and stable gene mutation[14].

The emergence and spread of drug resistant malaria motivated the search for new anti-malarial drugs over the last few decades.

As a result, different drugs[15], were developed (Table 5) to combat the scourge of this disease, halofantrene hydrochloride being the latest in this line of drugs[16-19]. This drug is a phenanthrene-methanol particularly effective in treating multi-resistant strains of plasmodium falciparum[20].

Orally administered halofantrine was found to be effective against both P. falciparum and P. Vivax. In all of the 32 patients treated with halofantrine, treatment resulted in a rapid disappearance of symptoms and parasitemia (<4 days). One of the

Table 5: Chemical classes of Anti - Malarials.

	Chemical Class Drug
1.	Cinchona Alkaloids Quinine
2.	9 - Aminoacridines Mepacrine
3.	4 - Aminoquinolones Chloroquine Amodiquine
4.	8 - Aminoquinolones Primaquine
5.	Biguanides Proguanil
6.	Diaminopyrimidines Pyrimethamine
7.	Sulfones Sulfonamides Dapsone Sulphalene
8.	Sulfantilfolates Sulphalene + Pyrimethamine Dapsone + Proguanil
9.	Antibiotics Miinocycline
10.	4 - Quinolinmethanols Mefloquine
11.	Sesquiterpene Lactone Qinghaosu (Artemesia)
12.	Phenantrene - Methanol Comp. Halofantrine Hydrochloride

major advantages of halofantrine is it's rapid onset of action. All of the patients, excepting one, became asymptomatic within 2-3 days of initiation of therapy. the one exception reported headache, itching 21 and nausea, which disappeared on the seventh follow-up day. The laboratory parameters including blood counts, renal function tests (urea, creatinine) and liver function tests did not demonstrate any abnormality at the seventh follow-up day.

Although there are a few reports in the literature, mentioning side effects such as transient diarrhea, dizziness, orthostatic hypotension[22], and cardiac conduction defects[23-25], no adverse effects secondary to therapy were observed in any of the 32 patients who received halofantrine in this study group.

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