EFFICACY OF HALOFANTRINE HYDROCHLORIDE IN VIVAX MALARIA

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ABSTRACT

Objective: To determine the efficacy of Halofantrine Hydrochloride in plasmodium vivax positive malaria.

Material and Methods: This study was conducted at DHQH Timergera, from January 2003-December 2003 and District Teaching Hospital, Dera Ismail Khan, from January 2004-December 2004. Patients presenting with fever and a laboratory diagnosis of plasmodium vivax in their blood were included in the study. Halofantrine Hydrochloride in tablet form was given in a dose of 500mg at six hourly intervals for three doses. Temperature record was kept and peripheral smear for malarial parasite vivax was done after 12 hours of the dose of Halofantrine and thereafter after every 24 hours for three consecutive days and again after 14 and 21 days for possibility of relapse.

Results: Of the 109 patients included in the study, 51 patients (46.79%) showed clinical response and their blood showed clearance of malarial parasite after three days of study. Fifty-eight patients (53.21%) did not clear up the malarial parasite and were still febrile after three days of therapy. Median fever clearance was 24 hours and median parasite clearance was also 24 hours. On follow-up, four (3.67%) of them relapsed in the three weeks and were still Pl. Vivax present in their blood. None of the patients reported adverse side effects.

Conclusion: Halofantrine, though a convenient drug has an efficacy of only 46.8%, a relapse rate of 3.7% and a failure of 53.21%. It should therefore be used with caution as malaria is a deadly disease.

Keywords: Malaria, Malaria Resistance, Halofantrine Hydrochloride, Plasmodium Vivax

INTRODUCTION

Malaria is the most important parasitic infection. It is known to be present in endemic form in at least 103 countries of the world. It affects more than one billion people per year and kills 1-3 million people every year.[1,2,3]

There is insecticide resistance of vectors and drug resistance of the parasite. This resistance is quickly emerging to even the new drugs and there is a great danger of endemicity even in non endemic areas.[4] Malaria has always been a threat to travelers while they travel to the endemic areas and it is present almost always as a pandemic in tropical countries.

In Pakistan malaria is endemic and resistance is very quickly developing to the drugs. Pakistan is present on the map of Chloroquine resistant malaria for a long time now and new drugs are needed to curb the infection.[5]

The two species, which cause malaria in Pakistan are: plasmodium vivax and plasmodium falciparum.[6] Plasmodium ovale and plasmodium malariae are virtually unknown.

Due to exo-erythrocytic cycle in the liver, plasmodium vivax but not plasmodium falciparum needs a radical cure with Primaquine after the initial antimalarials.[7]

Halofantrine hydrochloride is 9-phenanthrenemethanol, first identified as potential antimalarial agent by the World War II malaria chemotherapy program. It is schizonticidal with activity against the asexual erythrocytic stage of malaria and is considered as an oral alternative to chloroquine for the treatment of malaria due to plasmodium falciparum.[8] The company literature for medical professionals however, promotes and recommends its use for single or mixed infections of plasmodium falciparum or vivax. They however recommend primaquine (an 8-aminoquinolone) after vivax malaria to eliminate the hepatic forms. Tefanoquine is a new drug used as a potential alternative for primaquine for the treatment of recurrences.[9]

Halofantrine hydrochloride exhibits erratic bioavailability and absorption is significantly enhanced with fatty food. The elimination half-life is one to two days and is excreted mainly in the faeces. It has been shown to produce a dose-related prolongation of QTc interval and there have been rare reports of serious ventricular dysrhythmias sometimes associated with death. These cases can happen especially with the concomitant use of mefloquine, drugs which can cause a prolonged QT interval and congenital long QT syndrome. In addition to this it can cause nausea, abdominal pain, diarrhea, pruritis and skin rash as well as hemolytic reactions with renal failure and even convulsions have been reported.[8,9] Interestingly enough, these side effects have been mentioned in the prescribing leaflet of halofantrine[9] and this drug is not available in many countries including the United States. However this drug is very frequently used in Pakistan. This may be due to the convenience of dosage of this drug.

The objective of our study was to observe the efficacy of halofantrine in vivax malaria and to observe its side effects.

MATERIAL AND METHODS

The study was conducted in different time frames at two different hospitals, namely in District Hospital Timergera from January 2003 to December 2003 and at district teaching Hospital Dera Ismail Khan from January 2004 to December 2004. An informed consent was taken from all patients and a performa was used for recording all the observation. The patients were diagnosed as malaria after their blood film showed plasmodium vivax infection. None of the falciparum or mixed infections was included in the study. A baseline ECG was done for all patients to observe any possibility of a prolonged QTc interval.

Temperature was noted at 0 hours and ECG was labeled at 0 hours. Similarly the smear for vivax positive malaria was labeled at 0 hours. Patient was started at 0 hours with Halofantrine hydrochloride 500mg six hourly for three doses i.e. at 0, 6 and 12 hours.

Temperature record was maintained at 6 hourly intervals thereafter for three days and blood smear was observed at 18 hours and hereafter every 24 hours for presence of malarial parasite.

The patients who responded were observed again after fourteen and twenty-one days for possibility of relapse. At both of those visits, these were clinically examined and a blood smear was observed for malarial parasites on both occasions.

The patients who did not respond to halofantrine were put on alternative therapy which is not part of this study.

G6PD levels of all of these patients were checked and all except G6PD deficient patients were put on primaquine 15mg once daily for 14 days. This is in accord with the scientific regimen and is not a part of this study.

RESULTS

The number of cases at the two hospitals were almost equivalent i.e. fifty-nine patients at Timergera (30 males and 29 females) and fifty patients at Dera Ismail Khan (28 males and 22 females). The total number of male patients was 58 and female patients were 51. The age group was from 20 to 50 years in males with the mean age of 29 years. In female patients the age group was from 18 to 35 years with the mean age of 24 years.

Of the enrolled 109 patients, 51 patients (46.79%) showed clinical response and their blood showed clearance of malarial parasite after three days of study. Fifty-eight patients (53.21%) did not clear up the malarial parasite and were still febrile after three days of therapy. Median fever clearance was 24 hours and median parasite clearance was 24 hours. Follow-up of these patients showed that four (3.67%) of them relapsed in the three weeks

DEMOGRAPHIC FEATURES

Patients		Hospital I	Hospital II	Total
Total No		59	50	109
Male/Female		30/29	28/22	58/51
Age				
Male				
	Range:	20-50 Years	20-50 Years	20-50 Years
	Mean:	29	29	29
Female				
	Range:	18-35 Years	18-35Years	18-35 Years
	Mean:	24	24	24

Table 1

CLINICAL AND HAEMATOLOGICAL RESPONSE TO HALOFANTRINE

Patients	Hospital I	Hospital II	Total
Clinical Cure i.e. Afebrile, no complications	28(47.45%)	23(46%)	51(46.79)
Clinical Failure i.e. Febrile after three days	31(52.54%)	27(54%)	58(53.21%)
Laboratory Cure i.e. Negative blood smear for Vivax Malaria	28(47.45%)	23(46%)	51(46.79%)
Laboratory Failure i.e. Positive blood smear for Vivax Malaria	31(52.54%)	27(54%)	58(53.21%)
Recurrence i.e. Initial clinical and laboratory cure with late positive blood smear for Vivax Malaria (21 days follow up)	2(3.38%)	2(4%)	4(3.67%)
Long term responders i.e. Patients who initially responded and are still negative for Vivax Malaria on blood smear after 21 days of Follow-up	26(44.07%)	21(42%)	47(43.12%)
Total Patients	59(54.13%)	50(45.87%)	109(100%)

Table 2

of their out patient visits and were still having the malarial parasite (Pl. Vivax) in their blood. Long term response without a recurrence at or before three weeks was calculated at 47 patients (43.12%)

None of the patients reported adverse side effects. There was no effect on the QTc interval on ECG of any of these patients.

The study was done in two hospitals and except for the minor difference in the number of patients (59 against 50), no significant difference was found in both the places. The patients who responded to treatment in each hospital were 47.45% (28/59) and 46%(23/50) respectively. Two patients had a recurrence of malaria in each hospital with recurrence rate of 3.38% and 4% respectively which was also close to the cumulative result of both hospitals. The long-term response was also calculated as 44.07% (26/59) patients and 42% (21/50) respectively. Keeping these minor differences in mind, the efficacy was calculated cumulative for both hospitals.

DISCUSSION

Drug resistance is one of the major factors contributing to the resurgence of malaria, especially resistance to the most affordable drugs such as chloroquine and fansidar, a combination drug of pyrimethamine and sulfadoxine. Understanding the mechanisms of such resistance and developing new treatments, including new drugs, are urgently needed.[3] It is very evident from the review of literature that those antimalarials which were considered very effective in the last decade may no longer be effective in the present one and without studying the efficacy of these drugs, we may possibly miss the clue to their getting in effective. Getting few clinical failures usually does not prompt the busy physician to do such studies.

Plasmodium vivax is the most prevalent malaria infection and is an important cause of morbidity in Central and South America and Asia. P. Vivax is generally sensitive to the common antimalarial drugs but high level resistance to chloroquine and/or pyrimethamine has been documented in some geographic locations.[11]

Drug-resistant falciparum and vivax malaria will continue to be an increasing problem. The incidence of drug-resistant malaria has been increasing at a rate that exceeds new drug development. Plasmodium falciparum has rapidly developed resistance to new synthetic antimalarials, including mefloquine and halofantrine.[12] P. vivax malaria resistant to chloroquine and primaquine are now widespread in parts of Oceania; the optimal therapy for this infection is unknown. At present, a combination of Qinghaosu derivatives and mefloquine appears to be the most active drug regimen against multidrug-resistant falciparum malaria from Southeast Asia.

The capacity of pl. falciparum to rapidly develop drug resistance and the growing evidence that other plasmodia can evolve resistance suggests that within the next 10 years, we face the real

prospect of untreatable malaria. Ultimately, control of malaria may require more creative approaches than additional inhibitory drugs. These might include: the identification of biochemical pathways unique to the parasite (such as drug efflux and heme polymerase), making it possible to design new classes of antimalarial agents that are selectively toxic to the parasite; methods to block parasite development in the mosquito vector; and multistage vaccines against both asexual and sexual stages in order to block both the pathophysiology and transmission of disease.[12]

Halofantrine was originally marketed for chloroquine resistant malaria and the target was mostly plasmodium falciparum. It is however quite surprising that Halofantrine has always been used without any regard for its indication, probably due to the simplicity and convenience of its dosage. It is also interesting that this schizonticidal drug is not usually followed by a hypnocidal drug like primaquine for radical cure and the whole exercise becomes quite futile due to recurrence of the disease.

Resistance to quinine, Mefloquine and Halofantrine is still at low levels out of Thailand, as their use remains through medical hands. Non resistance was observed yet with artemisinin derivatives.[13] It is quite evident that resistance to Halofantrine was on the cards for long because of the irrational use of this drug and its use by non professionals. In Pakistan the issue of usage of non-prescribed drugs is immense and if unchecked, will lead to resistance of the most standard medication.

Drug resistance is a major problem in malaria. The resistance mechanism remains unresolved but contributing factors are probably heavy drug use, parasite selection, cross-resistance and genetic influences of drugs. P. vivax has chloroquine resistant strains, mefloquine resistance is a problem mainly confined to Thailand. There is cross-resistance between halofantrine and mefloquine. Decreased sensitivity to quinine was reported from Thailand, but it remains an effective drug, notably when given in combination with tetracycline or doxycycline. In cases of severe or complicated malaria intravenous quinine is still the preferred therapy. Resistance to artemisinin has not yet been reported. Pharmaceutical companies show little interest in antimalarial drug development, which in view of the increasing drug resistance is a matter of great concern.[14]

Although more than 40% of the world's population lives in malaria endemic areas, there are only 6 available antimalarial drugs for the treatment of plasmodium falciparum infections. Three of these have been developed in the last 20 years. Halofantrine is also well tolerated and has a rapid antimalarial activity but there is a known cross-resistance with mefloquine. The discovery of a potentially lethal cardiotoxicity associated with halofantrine casts a further shadow over its use. The artemisinin derivatives represent an exciting breakthrough in the treatment of malaria. They are cheap and have a very rapid action. They seem remarkably free from toxic adverse effects, although the neurotoxicity seen in animal studies with the liposoluble derivatives gives rise for concern. However, the lack of pharmacokinetic and toxicity data as yet preclude their approval by western drug regulation authorities. All antimalarials are threatened by the emergence of parasite resistance. Combination therapy using mefloquine and an artemisinin derivative may provide a way in which resistance can be combated.[15]

Halofantrine is an orally administered blood schizontocide which is active against both chloroquine-sensitive and chloroquine-resistant plasmodia. Dose-finding and no comparative clinical trials have confirmed the efficacy of halofantrine in the treatment of falciparum malaria in areas of chloroquine and sulfonamide/ pyrimethamine-resistant malaria and vivax malaria. However, poor results obtained in patients who failed Mefloquine prophylaxis suggest that the efficacy of halofantrine may not extend to mefloquine-resistant P. falciparum, although more studies are needed to confirm this. Data concerning halofantrine in the treatment of P. ovale and P. malariae infections are still limited. One comparative study indicates that halofantrine has an efficacy equivalent to that of mefloquine and may be better tolerated. Halofantrine is generally well tolerated in adults and children, the most common drug-associated effects being abdominal pain, pruritus, vomiting, diarrhoea, headache and rash, although it is difficult to distinguish between disease- and treatment-related events. The development of parasite resistance to halofantrine, like other blood schizonticides, is inevitable. Poor absorption resulting in variable peak plasma halofantrine concentrations, and possible cross-resistance with mefloquine, may accelerate the emergence of resistance to halofantrine. Thus, it is of primary importance that halofantrine is used only in areas where chloroquine- and sulfonamide/pyrimethamine-resistance are established in order to preserve and sustain its efficacy. If used with care, halofantrine will provide an important treatment option for falciparum malaria, a widespread parasitic disease associated with considerable morbidity against which the number of effective drugs available is being increasingly compromised by the spread of resistance.[15]

There was a recently published study from Pakistan which had almost contradictory results compared to ours.[16] They gave an efficacy of 97% for halofantrine against ours 47% and a relapse rate of 1% against our 3.67%. It maybe due to the different localities of the study. The study is however, comparable to our study in terms of the safety profile.

Some studies recommend a repeat dosage of halofantrine at 7 days after the first dosage. This may be a clue to the inadequacy of a previously devised dosage regimen. There was a relapse of 12.2% in patients who received single therapy but no relapse was reported after the second dosage after 7 days of first dosage.

CONCLUSION

Our study proves that resistance has been developed to halofantrine and alternative therapy should always be kept in mind. Less toxic and more effective drugs are available and probably they should be used. Convenience should not be the sole reason of its use and effectiveness should be the criteria for treating malaria. It should not be misused still as it may be effective in its original indication for chloroquine resistant or multi-drug resistant Falciparum infection. The drug like any other drug should only be used on prescription.

If at all it is to be used, the dosage may be rescheduled for halofantrine and a second dosage at 7 days may reduce the number of recurrences. It should be followed by primaquine as a hypnocidal drugs in people who's G6PD is normal.

Research should be put into malaria treatment, as we are not left with many drugs in our armamentarium.

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