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QT PROLONGATION WITH THE USE OF ORAL ARTEMETHER-LUMEFANTRINE COMBINATION THERAPY

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Contribution

MS conceived the idea and designed study. MAK, AZ and SAS did data collection and manuscript writing. SU analyzed data. UA did review. All authors contributed equally to the submitted manuscript.

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ABSTRACT

Objective: To determine the frequency of patients developing QT prolongation with the use of oral Artemether-Lumefantrine (AL) combination therapy

Methodology: This cross sectional study was conducted in general medicine department of Khyber Teaching Hospital from January to December 2018. A total of 133 patients were selected on basis of consecutive (non-probability) sampling. All adult patients (irrespective of gender) presenting with high grade fever having positive blood smear (thick and thin blood films) for plasmodium falciparum and not taken any antimalarial treatment in the preceding seven days were included in the study. All information was entered in pre designed proforma.

Results: Total 133 patients were including. Mean age was 30 ± 3.18 years. About 72% patients were males while 28% patients were female. Prolong corrected QT interval among 133 patients were analyzed, and no patient with prolonged corrected QT interval was observed.

Conclusion: It can be concluded that AL is a safe drug combination for the treatment of falciparum malaria with negligible adverse effects on QT profile.

Key Words: QT Prolongation, Plasmodium falciparum, Malaria, Artemether, Lumefentarine.

INTRODUCTION

Malaria is the most important parasitic disease of humans causing hundreds of millions of illnesses and nearly a million deaths each year.[1] The current World Health Organization (WHO) guidelines for the treatment of malaria recommend the use of artemisinin based combination therapy (ACT) owing to the rising threat of Plasmodium falciparum resistance to monotherapy.[2] Artemether/Lumefentarine (AL) was the first fixed-dose combination of ACT to be approved by the European regulatory authorities according to the requirements of the International Committee on Harmonization.

Several antimalarial can cause significant prolongation of the electrocardiograph QT interval, which can be associated with an increased risk of potentially lethal ventricular arrhythmias. High doses of Artemether and Artemotil have been associated with QT prolongation in dogs, raising the possibility of a class effect with the artemisinin derivatives. Serial electrocardiograms were recorded, and QT interval was calculated before and after administration of artesunate by intravenous injection in patients with severe falciparum malaria in Bangladesh. Intravenous artesunate does not have significant cardiovascular effects in patients with severe falciparummalaria.[3]

Since the 1960s, chloroquine-resistant and multidrug-resistant strains of *P. falciparum* have emerged in Africa and Southeast Asia and have spread worldwide. Newer anti-malarial drugs were developed including mefloquine, a 4-quinoline methanol similar to quinine, and halofantrine, a 9-phenanthrene methanol structurally related to quinolone anti-malarial drugs. Because both drugs are administered orally, their widespread use was anticipated for the treatment of uncomplicated cases of drug-resistant P. falciparum infection. However, in 1993, reports of severe and sometimes fatal cardiotoxicity associated with the use of halofantrine led the World Health Organization to limit its use and as of 2002, there were at least 20 reports of fatal cardiac complications relating to use of the drug. These events were attributed to a QT prolongation effect of halofantrine, identified in several human studies of the drug. These unexpected cardiac problems resulted in the withdrawal of the drug from the market in many countries except Pakistan and parts of West and Central Africa and underlines the importance of examining the cardiotoxic potential of quinolone and other structurally related anti-malarial drugs before the wider marketing of newer drugs.[4]

The rationale of this study was that the earliest available drugs of Artemether combination therapy i-e Halofantrine were withdrawn from the market few years ago due to their serious cardiotoxicity and ventricular arrhythmias because of their effect on QT interval prolongation, Being a drug of that class, Artemether combination therapy also has theoretical potential of QT interval prolongation. Being resident in malaria endemic zone we are using Artemether combination therapy without taking into consideration of these serious effect.

The purpose of this study is to find out the frequency of QT interval prolongation in patients with falciparum Malaria treated with Artemether-Lumefentarine combination.

METHODOLOGY

This cross sectional study was conducted in General Medicine Department of Khyber Teaching Hospital from January 2018 to December 2018. The duration of the study was one year. 133 patients were selected on basis of consecutive (non-probability) sampling. All adult patients (irrespective of gender) presenting with high grade fever having positive blood smear (thick and thin blood films) for plasmodium falciparum and has not taken any antimalarial treatment in the preceding seven days were included in the study. Those patients were excluded from the study who had congenital QT interval prolongation, who were on drugs (Amiodarone, sotalol, Tricyclic antidepressants, fluoxetine, chloroquine, erythromycin and terfenadine) that cause QT interval prolongation and patients who had hypokalemia or hypocalcemia. All information was entered in pre designed proforma.

Patients were admitted in hospital to ensure drug compliance and for investigations. Blood samples was taken for routine hematology and biochemistry analysis inclusive of complete blood count, platelet count, blood glucose fasting and random levels, serum urea and creatinine levels, urine for routine examination and microscopy, and serum for liver function tests and electrolytes.

Treatment was started with a six dose regimen of oral Artemether-Lumefantrine (AL) combination therapy with each dose of 80/480mg. Vital signs ware recorded every 6 hours until resolution of fever and thereafter every 6 to 12 hours. Electrocardiography was done before starting the patients on oral AL and QT interval was calculated. Corrected QT interval (QTc) was calculate using Bazett's formula.[5]

$$Qtc\ (s) = QT\ interval / \sqrt{RR\ interval}$$

The patients were examined twice daily for any adverse effects of the drug or for the development of any complications of the disease. Repeat ECG was done every 24hours after starting the therapy.

Approval was obtained from ethical committee of the hospital. Data was analyzed using SPSS version 22.

RESULTS

Total 133 patients were included. Mean age was 30 ± 3.18 years. Age distribution among 133 patients was analyzed as 32(24%) patients were in age range 20-30 years, 44(33%) patients were in age range 31-40 years, 40(30%) patients were in age range 41-50 years and 17(13%) patients were in age range more than 51-60 years (Table 1). There were 72% (n=96) male while 28% (n=37) patients were female.

Prolongation of QT interval at 24 hours, 48 hours and 72 hours. Mean duration of QT interval was 0.38 ± 1.13 second is shown in table 2. Prolong corrected QT interval among 133 patients was analyzed as no patients had prolonged corrected QT interval. (Table 3). Chi square test was applied and post stratification of prolong corrected QT interval with age and gender was 0.003 and 0.002 respectively. ($p < 0.05$).

Table 1: Age Distribution study population (n = 133)

AGE	Frequency (%)
20-30 years	24% (n=32)
31-40 years	33% (n=44)
41-50 years	30% (n=40)
51-60 years	13% (n=17)

Table 2: QT Interval study population (n = 133)

	QT Interval	Frequency (%)
24 hours ECG	380-420	100%(n=133)
	> 420	0
48 hour ECG	380-420	100%(n=133)
	> 420	0
72 hour ECG	380-420	100%(n=133)
	> 420	0

Table 3: Prolong Corrected QT Interval study population (n = 133)

QT	Frequency (%)
Prolong Corrected QT	0
Yes	100%(n=133)
No	

DISCUSSION

Among blood infections, malaria is the most widespread public health problem of the tropics with its morbidity and mortality at unacceptable high levels in the region. Falciparum and vivax malarias are major health problems in Pakistan. In the last decade, there has been a six folds increase in falciparum malaria, which now comprises 42% of all malaria cases recorded by National Malaria Control Program, Pakistan.[6]

Pakistan is a tropical and agricultural country with urbanized population of 35%. 65% of its population is living in rural areas with widespread irrigation system. Annual floods in the rivers coupled with monsoon season and inadequate waste disposal all over the country, offer a suitable scenario for malaria transmission.[7]The incidence of malaria in urban settings is a growing concern in many regions of the world and the overall prevalence of malaria has decreased from 15.57% in 1960 to 0.45% in 1979.[8]

Our study shows that 24% patients were in age range 20-30 years, 33% patients were in age range 31-40 years, 30% patients were in age range 41-50 years and 13% patients were in age range more than 51-60 years. Mean age was 30 years with SD + 3.18. Seventy two percent patients were male while 28% patients were female. Prolong corrected QT interval among 133 patients was analyzed as no patients had prolong corrected QT interval. Similar findings were also observed in another study conducted by Bazzet HC et al in which a total of 200 patients aged between 14-67 years were included in the study. Amongst them, 110 (55%) were male and 90 (45%) were female.[5] Patients had a QTc ranging from 0.34s to 0.46s before the start of quinine therapy (Table 1). Following oral AL therapy, none of the patients were noticed to have QTc prolonged beyond the normal range that could warrant discontinuation of treatment (Table 2). A comparison of the mean QTc before and after treatment with oral AL combination therapy.

The results of our study show that AL combination therapy is safe regarding its cardiac profile. Similar conclusion was made in a study carried out by Vugt and colleagues in which the effect of AL combination therapy on QT interval at different serum concentrations of AL was judged and the cardiotoxicity of this drug combination was minimal.[9] There has been natural concern over the cardiotoxic potential of newly introduced antimalarial drugs since the unexpected discovery of the marked effects of halofantrine on ventricular repolarization, well after it had been introduced in clinical practice. Electrocardiogram QT prolongation is a well-known risk factor for pro-arrhythmic events, including sudden death. Lumefantrine is an aryl-amino alcohol antimalarial with some structural similarities to halofantrine. It is also, like halofantrine, lipophilic and hydrophobic, with very variable oral bioavailability leading to considerable inter-individual variability in plasma concentrations. However, unlike halofantrine, it proved to have no detectable cardiac effects over a wide range of plasma concentrations. In this study, there was no discernable change in the electrocardiographic QT interval after starting antimalarial treatment. Generally, small changes in QTc interval were noted, but they were similar to those reported in patients with malaria

treated with other antimalarial drugs (and much less than those recorded after treatment with drugs known to prolong the QT interval). There has been debate recently whether malaria itself affects ventricular repolarization. Small but significant differences have been observed in the QT interval corrected by Bazett's formula between acute malaria and convalescence.[10]These are associated with a decrease in heart rate associated with defervescence. Dividing the QT interval by the square root of the R-R interval does not correct adequately for changes in heart rate since heart rate and QT/ÏRR remain significantly correlated.[11] Thus, the apparent malaria effect on ventricular repolarization may simply reflect heart rate changes. In any case, the effects are very small.

A study carried out in India also pointed out that if artemether and lumefantrine had any significant effects on cardiac conduction or repolarization, then there should have been a relationship between concentration and effect, but none was found in the study.[12] No correlation between the length of the QTc interval and plasma drug concentrations was found in the study. In fact, the study observed that the QTc interval was decreased after dosing of AL combination therapy.

Patients with pre-existing repolarization abnormalities may be more vulnerable to factors that prolong the QT interval. In this series, there was no relationship between baseline QTc interval and the fractional increase. Overall, these data provide strong evidence against a systematic effect of therapeutic doses of Lumefentarine on cardiac conduction or repolarization.

CONCLUSION

It has been well recognized that a prolonged QT interval (congenital or acquired) on the surface ECG is associated with an increased risk of Torsade's de Pointes and/or sudden death. By far the most common cause of acquired long QT syndrome is drug induced, with antimalarial being one of the most commonly implicated drug group. The results of our study reveal that the risk of QT interval prolongation with AL combination therapy is negligible, and it can be safely used for the treatment of malaria especially in malaria endemic areas where the parasite has acquired resistance to many conventional drugs. The risk of Torsade's de Pointes associated with prolonged QT interval is still likely to remain a significant problem in the future and further research on this issue is warranted.

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