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ORIGINAL ARTICLE

Prolongation of QT Interval as a Result of Combination Therapy of Oral Artemether-Lumefantrine: A Cross-Sectional Study

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ABSTRACT

Aim: To determine the frequency of prolongation of QT interval as a result of combination therapy of oral Artemether-Lumefantrine

Study design: A cross-sectional study

Place and Duration: This study was conducted at Karachi Institute of Heart Diseases Karachi Pakistan from June 2020 to June 2021.

Methodology: The study included a total of 120 participants. Participants were selected by a consecutive sampling method. All the patients were adults and had been diagnosed with malaria by positive blood smear for plasmodium falciparum. The patients had not taken any antimalarial therapy for the last seven days of reporting to the hospital. The treatment was given in six doses of AL combination therapy. The strength of one dose was 80 mg Artemether and 480 mg of Lumefantrine. The QT interval was calculated before and after the therapy administration. Bazett's formula (Qtc (s) = QT interval / √ RR interval) was used for the calculation of the corrected QT interval (Qtc)

Results: The mean age of the patients was 30 ± 2.96 years. A total of 85 (70.83%) were male and 35 (29.17%) were female. According to the age distribution, 31 (25.83%) patients were between the age of 20 years and 30 years. A total of 42 (35%) patients were between the age of 31 and 40 years. 36 (30%) were in the age range of 41 and 50 years. A total of 11 (9.17%) were above the age of 50 years All the patients were analyzed for QT interval prolongation and the QT interval was not prolonged in any of the participants.

Conclusion: As QT interval prolongation was not observed in any of the patients, oral AL can be considered a safe combination therapy for the treatment of malaria caused by plasmodium falciparum.

Keywords: Artemether, Lumefantrine, QT prolongation, Malaria, Plasmodium Falciparum

INTRODUCTION

Malaria is a common parasitic disease, especially in third-world countries. It causes illness in millions of people annually. It is also responsible for millions of deaths each year. Nearly half of the population of the World lives in the areas at risk of transmission of malaria [1]. According to the recent guidelines of the World Health Organization (WHO), the recommended treatment for malaria is artemisinin combined therapy (ACT) [2]. This treatment is preferred due to the resistance of plasmodium falciparum to monotherapy. Artemether-Lumefantrine (AL) was the first combination therapy of ACT that was approved according to the International Committee on Harmonization requirements.

There are some antimalarial drugs that can result in QT interval prolongation on electrocardiography. This adverse effect has the potential to cause severe ventricular arrhythmias that can also be lethal. High potency doses of Artemotil and Artemether have been seen to cause prolongation of QT intervals in dogs. Artemisinin derivatives cause similar effects. A study was conducted in which electrocardiograms were performed before and after the administration of artesunate. The drug was injected intravenously in the diagnosed patients with malaria caused by plasmodium falciparum. The QT interval of the patients was calculated before and after giving the drug. The therapy did not have any significant effects on the cardiovascular system of the patients [3].

Out of all the antimalarial drugs, halofantrine is the most notorious cardio-toxic drug. That is why its use had been restricted by WHO in 2002 after almost 20 fatalities. This drug is associated with prolonged QT intervals. The cardiotoxicity of quinolones and other antimalarial drugs that were structurally related to quinolones had raised concerns about other antimalarial drugs as well [4]. As Artemether is also from the same drug class, it is also thought to cause prolonged QT intervals. The purpose of our study is to find out the frequency of prolongation of QT interval in malaria patients treated with AL combination therapy.

METHODOLOGY

Our study is a cross-sectional study including 120 patients. All the patients were selected by consecutive non-probability sampling. All the patients considered in the study were adults. Permission was taken from the ethical review committee of the institute. The patients included in the study had presented with high-grade fever. They had been tested positive for plasmodium falciparum through a thin and thick blood smear. According to the inclusion criteria, only those patients were included that had not taken any other antimalarial therapy in the last seven days of presentation in the hospital. Patients having congenital prolonged QT intervals were not included in the study. Those patients that were already taking drugs that can cause QT interval prolongation such as fluoxetine, tricyclic antidepressants, amiodarone, erythromycin, sotalol, terfenadine, and chloroquine, were not considered in the study. Moreover, hypokalemic and hypocalcemic patients were not added to the study. The data of the patients were collected and recorded in an individual proforma.

For regular monitoring through investigations and ensuring compliance with the drug, patients were admitted to the ward. Blood samples of all the patients were collected at the time of admission for hematology and biochemistry. The laboratory investigations ordered for all the participants were complete blood count, blood glucose in fasting as well as random state, serum urea, serum creatinine, urinalysis, microscopy of the blood, platelet count, electrolytes, and serum liver function tests.

The treatment was given in six doses of AL combination therapy. The strength of one dose was 80 mg artemether and 480 mg of lumefantrine. The vitals monitoring was done every 6 hours until the fever resolved. Electrocardiography of all patients was done before and after the administration of the therapy. Similarly, the QT interval was also calculated before and after the therapy administration. Bazett's formula (Qtc (s) = QT interval / √ RR interval) was used for the calculation of the corrected QT interval (Qtc) [5].

The patients were checked for hypersensitivity reactions or adverse effects and other complications of the drugs twice daily. The electrocardiogram of all the patients was done every 24 hours. The data were analyzed in IBM SPSS version 26.

RESULTS

A total of 120 patients were considered in the present study. The mean age of the patients was 30±2.96 years. According to the age distribution, 31 (25.83%) patients were between the age of 20 years and 30 years. 42 (35%) patients were between the age of 31 and 40 years. A total of 36 (30%) were in the age range of 41 and 50 years. A total of 11 (9.17%) were above the age of 50 years. The age distribution has been shown in Table 1.

There were 85 (70.83%) male patients and 35 (29.17%) female patients. Prolongation of the QT interval was calculated 24 hours after the administration of a drug, and then after 48 and 72 hours. The mean of the QT interval was 0.38±1.25. The findings are shown in Table 2. None of the patients had been noticed with a prolonged QT interval. A Chi-square test was applied. Post-stratification of gender was 0.002 and that of the prolonged corrected QT interval was 0.003 ($p < 0.05$).

Table 1: Age distribution of the patients (n=120)

Age (years)	Frequency	Percentage
20-30	31	25.38
31-40	42	35
41-50	36	30
>50	11	9.17

Table 2: Study of QT interval in the population under study (n=120)

Time of ECG	QT interval	Frequency	Percentage
24 hours	380-420	120	100
	> 420	0	0
48 hours	380-420	120	100
	> 420	0	0
72 hours	380-420	120	100
	> 420	0	0

DISCUSSION

Malaria is the most common blood infection in tropical regions. It has a high rate of morbidity and mortality. Vivax and falciparum are major health issues in the community of Pakistan. According to the survey by the National Malaria Control Program of Pakistan, the ratio of falciparum increased by six folds in the last decade. Moreover, 42% of the cases of malaria found in Pakistan are falciparum malaria.

Pakistan is an agricultural and tropical country. The urbanized population of Pakistan is 35% while 65% of is residing in rural areas. The irrigation system of these areas, annual floods, monsoon rains, and inadequate disposal of waste are suitable environments for the transmission of malaria [7]. However, the increasing incidence rate of malaria transmission in urban settings is also concerning in many countries of the world. Nonetheless, the prevalence of malaria decreased from 15.57% to 0.45% from 1960 to 1970, respectively [8].

Our study shows that AL combination therapy for the treatment of malaria does not affect the QT interval, contrary to the theoretical concept that artemether can be cardio-toxic. Another similar study was carried out by Adjei et al in which 77 participants were considered. A total of 47 of them were treated with artesunate-amodiaquine while 30 were treated with an AL combination. The ECGs of the patients were performed before and after the treatment administration. It was noted that children treated with artesunate-amodiaquine had developed sinus bradycardia. They concluded that no rhythm disturbance was seen in patients treated with AL combination therapy [9]. Hence, the result of our study is consistent with the study of Adjei et al.

Wu et al studied the effect of three combination therapies on the cardiac rhythms of the patients. Those three combinations were artemether-lumefantrine (AL), artemisinin-piperaquine (AP), and dihydroartemisinin-piperaquine (DP). Electrocardiograms of all three groups were recorded before and after the administration of the medical therapy. Those ECGs showed that all three regimens had a mild effect on the QT interval. Therefore, they concluded that prolongation of QT interval is seen in all the regimens of malaria, however, this cannot lead to arrhythmias [10].

A study was conducted by Lefèvre et al to find out the cardiac effects of AL combination therapy overlapping with the quinine drug in patients that have been diagnosed with malaria caused by multi-drug resistant plasmodium falciparum. It was observed that if quinine and AL are given simultaneously, they have a minor effect on the QT interval. They had concluded that the benefits of the combination therapy outnumber its adverse effects [11]. Their results were different compared to the results we obtained in the present study. The study of Bindschedler et al also shows that the QT prolongation is insignificant in the patients treated with the AL combination therapy [12].

Most of the studies carried out to determine the cardiac effect of AL combination have proven that the prolongation of QT interval is rare after this therapy. Combining AL therapy with any other antimalarial drug can interfere and bring cardio-toxic effects.

CONCLUSION

The results of the present study revealed that prolongation of QT interval is not associated with the administration of AL combination therapy. Hence, it can be administered safely in patients with plasmodium falciparum malaria. Likewise, the risk of Torsade's de Pointes which is associated with the prolonged QT interval is also less likely to happen. Furthermore, future researches are necessary in this regard and they may show different results.

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Conflict of interest: The present study did not have any kind of conflicts of interest

Permission: Permission was asked for and taken from the ethical committee of the institute

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