ORIGINAL ARTICLE

ANALYTIC STUDY IN PATIENTS PRESENTING TO A TERTIARY CARE HOSPITAL REGARDING THE ARTEMETHER-LUMEFANTRINE INDUCED QTc INTERVAL CHANGES IN ECG

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Background: Malaria is one of the most common causes of morbidity and mortality in our part of the world. Artemether-Lumefantrine (AL) Combination therapy is widely used for the treatment of malaria both in outpatients and inpatients hospital settings. Some of the previous anti-malarial were associated with prolongation of QT_c interval. Similar query was raised about AL therapy. This study was conducted to determine the risk of QT_c interval prolongation in ECG of patients with Falciparum malaria using oral Artemether-Lumefantrine (AL) combination therapy. **Methods:** The venue of this analytical, quasi-experimental study was Medical Unit A, Khyber Teaching Hospital Peshawar, spanning 1st August 2015 to 31st July 2016. The study sample included male and female patients, having Plasmodium falciparum rings in their peripheral smear. These patients were treated with oral Artemether- Lumefantrine (AL) combination for 3 consecutive days in recommended doses. Electrocardiography (ECG) profile before and after 72 hours' treatment with AL was noted for discernable QT_c interval changes. The calculated prolongation of the QT_c interval between these two study points was analyzed using Paired samples *t*-test. The statistically significant P value for this study was 0.05. SPSS version 23 was used for statistical analysis. **Results:** Amongst 200 cases, the QT_c interval was noted to be normal before the start of the treatment in all. There was no significant prolongation of QT_c interval following the treatment (*p*-value=0.119) in the treated patients. It appears that cardiotoxicity is a remote adverse effect of AL combination therapy and that its use is safe in patients with Falciparum malaria. **Conclusion:** It can thus be concluded that AL is a safe drug combination for the treatment of falciparum malaria with negligible cardiotoxic adverse effects.

Keywords: Artemether- Lumefantrine (AL) combination Therapy; QT_c interval; Arrhythmia; Cardiotoxicity

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INTRODUCTION

Malaria is amongst the major causes of morbidity and mortality worldwide especially in the developing countries accounting for about 0.9 million deaths annually.[1] According to the recent World Health Organization (WHO) guidelines, Artemisinin based Combination Therapy (ACT) is the linchpin in the treatment of malaria owing to the rising incidence of resistance of Plasmodium falciparum to monotherapy.[2] Based on the recommendation of International Committee on Harmonization (ICH), the European Regulatory Authority was the first to approve (AL) as the first fixed-dose combination of ACT. It merits description that AL is also recommended by the WHO for its efficacy, safety and quality specifically as a six-dose regimen for infants, children and adults with acute, uncomplicated or mixed P. falciparum infections.[3,4] The efficacy of (AL) combination has been proved in multiple studies across the world involving patients from different races and ethnicities.[5]

Lumefantrine is recognized chemically as 2-dibutylamino-1-[2,7-dichloro-9-(4-chlorobenzylidene)-9H-fluoren-4-yl]-ethanol and is a racemic fluorene derivative. It is structurally related to other antimalarials like halofantrine, quinine and mefloquine. Among the antimalarials, quinine, quinidine and halofantrine are known causes of QT_c interval prolongation even when used in therapeutic dosage.[6,7] Halofantrine has been associated with sudden death due to this same cause and is accordingly withdrawn by FDA.[7,8]

Artemether, derived from artemisinin is chemically a methyl-ether derivative of di-hydroartemisinin. It along with a related compound, arte-ether, when given in high doses intramuscularly is known to prolong the QT_c interval in rats and dogs.[9] This raised a concern that similar effects could occur on its clinical use in humans also. However, evidence from large prospective clinical trials disproved of its cardiotoxicity in human beings.[10,11]

AL combination is given in a 4-dose regimen, made up of a total of 320 mg of Artemether and 1,920 mg of Lumefantrine in adults. Two studies in Thailand, conducted with a 6-dose AL regimen produced better results than the

4-dose AL regimen with no additional toxicity profile.[12,13] This dose–optimizing with higher dose regimens provided an opportunity to conduct detailed electrophysiological studies and to relate any changes to the plasma concentration of individual components.

Our study was based on the above rationale trying to measure the effect of AL on the QT_c interval in the setting of our tertiary care hospital. Patients with malaria who were smear positive for P. Falciparum were usually treated with parenteral quinine in our hospital. Our study aimed to demonstrate whether the results obtained by our model could be used to predict the cardiotoxicity of AL when used in our clinical settings.

MATERIAL AND METHODS

An analytical, quasi-experimental study was conducted in Medical "A" unit of Khyber Teaching Hospital, Peshawar, Pakistan over a period of 12 months from August 1st 2015 to July 31st 2016. Approval was taken from the Hospital Ethics Committee before conducting the study. A written informed consent was obtained prior to enrollment in our study and a detailed proforma was used to record the data. The study sample included both genders aged 14 years and above, who presented with high grade fever associated with rigors and chills, positive peripheral blood films for Plasmodium Falciparum under light microscopy and who had not taken any other anti-malarial medications in the last 7 days. Patients not satisfying these criteria were excluded from the study. Patients justifying the inclusion and exclusion criteria were admitted to our Medical unit as part of our protocol to ensure data collection.

After detailed history and physical examination, the data were recorded on an approved questionnaire. Blood samples taken for routine hematology and biochemistry analysis were especially marked to the hematologist for the detection of various rings of plasmodium species. Once Plasmodium Falciparum was confirmed as the cause of fever, treatment was started with a six-dose conventional (AL) combination regimen. Supportive treatment included oral acetaminophen to patients with temperature more than 101°F. Patients were assessed periodically for Vital signs till the resolution of the fever and thereafter. Electrocardiography was carefully recorded before starting the patients on oral AL and three days after the AL therapy. QT interval including Corrected QT interval (QT_c) were calculated using Bazett's formula:[14]

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

Normal range of corrected QT interval was taken as 0.35–0.46 sec.

The cases were specifically followed for the development of any complications of the disease or the treatment.

For the categorical variables, such as gender and age frequencies and percentages were calculated, whereas for continuous variables like Hemoglobin, Total Leukocyte Count, Platelet count, Bilirubin, Alanine transaminase, Alkaline phosphatase, Urea, Creatinine, Sodium, Potassium and Chloride, mean±standard deviation were calculated. Corrected QT interval was expressed as frequency, percentage and mean±standard deviation. Paired samples t-test was used for comparison of QT interval before and after AL treatment. A *p*-value of <0.05 was taken to be statistically significant for our study design. Latest SPSS version 23 was used for data analysis.

RESULTS

Out of the total 200 collected cases, aged 4–67 years, 110 (55%) were male and 90 (45%) were female. The QT_c ranged from 0.34– to 0.46s before the start of AL therapy (Table-1). After the oral AL therapy, QT_c prolongation to the extent which would warrant discontinuation of AL combination therapy was not noted (Table-2). A comparison of the mean QT_c before and after treatment with oral AL combination therapy as shown in table-2 clearly demonstrated that there is no significant difference between QT_c interval before and after AL combination treatment (*p*=0.119).

Table-1: Baseline Patients' Characteristics

Characteristics	Frequency (n=200)	Percentage
Gender		
Male	110	55.0
Female	90	45.0
Age (years)		
<= 20	18	9.0
21–30	35	17.5
31–40	44	22.0
41–50	64	32.0
>50	39	19.5
	Mean	**SD**
Hb (g/dl)	11.73	1.51
TLC (10^3 /mm^3)	6.36	3.07
Platelets (x10^5/mm^3)	2.07	1.2
Bilirubin (mg/dl)	1.06	0.49
ALT (IU/l)	31.10	12.32
ALP (IU/l)	183.72	59.21
Urea (mg/dl)	31.89	9.51
Serum Creatinine (mg/dl)	0.99	0.21
Serum Sodium (mEq/l)	134.71	6.06
Serum Potassium (mEq/l)	3.66	0.42
Serum Chloride (mEq/l)	100.28	5.05

Table 2: Corrected QTc interval before and after AL treatment

Characteristics	Frequency (n=200)	Percentage
Before treatment (seconds)		
0.34	4	2.0
0.36	28	14.0
0.38	20	10.0
0.4	58	29.0
0.41	19	9.5
0.42	43	21.5
0.43	8	4.0
0.44	19	9.5
0.46	1	0.5
	Mean	**SD**
Average	0.4	0.03
After treatment (seconds)	**Frequency**	**Percentage**
0.34	7	3.5
0.36	31	15.5
0.38	24	12.0
0.4	59	29.5
0.41	22	11.0
0.42	38	19.0
0.43	6	3.0
0.44	13	6.5
	Mean	**SD**
Average	0.397	0.03
	p*-value	
Comparison of QT interval before and after treatment	0.119	

**p*-value calculated by paired samples *t*-test

DISCUSSION

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_c interval at different serum concentrations of AL was judged and the cardiotoxicity of this drug combination was minimal.[15] The concern in medical circles after the discovery of QT_c prolongation and the resultant mortality due to the much talked about Halofantrine raised many eye brows, making the physicians defensive on undertaking any risk with a new drug from related group or classes.[7,8,14,16,17] Pathophysiologically QT_c prolongation is well known to cause arrhythmia culminating in serious adverse effects including sudden death. While Lumefantrine is structurally related to halofantrine and shares with it pharmacokinetic profiles like lipophilicity and hydrophobicity and variable oral bioavailability, however, unlike halofantrine, it has a proven safe cardiac profile.

This study proves beyond doubt that there is no QTc interval prolongation with AL combination. The small changes in QT_c interval noted with AL based regimen are in fact no worse than other conventional anti-malarial drugs and are in fact much less than those drugs with known tendency to prolong QT interval. There is recently a debate as to whether malaria itself might affect ventricular repolarization. Studies however give little credence to such hypotheses.[16] The small changes themselves might be due to changes in the heart rate once the acute febrile illness is on or over.[18,19] The proposed apparent effects of malaria on ventricular repolarization should therefore be discarded and overlooked.

This above conclusion was reinforced by a study in India which questioned that in case there is any significant effect on cardiac conduction or repolarization due to AL based therapy then there should have been a linear dose response curve but the facts point towards the opposite.[20] In fact there is no correlation between the length of the QT_c interval and plasma drug concentrations and surprisingly according to this study, the QT_c interval decreased after AL combination therapy.

A logical conclusion thus inferred recommends that pre-existing repolarization abnormalities should not be discounted while arriving at a conclusion about the QT interval related to anti-malarial drugs. Lumefantrine in the AL combination should therefore be counted as having much better safety profile than Halofantrine and others.

CONCLUSION

A prolonged QT interval (congenital or acquired) ECG is always arousing curiosity in physicians as it is associated with a preventable risk of serious arrhythmias and sudden death. Anti-malarials are most commonly implicated among the acquired causes. The results of our study however prove that the risk of QT_c interval prolongation with AL combination therapy is negligible and it can be safely used for the treatment of malaria especially in malaria endemic areas especially where resistance to conventional antimalarials is common. The reported link to the risk of torsades de pointes associated with prolonged QT interval, which is linked to AL combinations is unfounded. Further research on the subject is however recommended.

AUTHORS' CONTRIBUTION

AB: Materials and Methods, Data collection and discussions. IH: Compilation of data into results, Reference writing. SS: Literature review.

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