CHLOROQUINE AND AZITHROMYCIN INDUCED QTC PROLONGATION IN COVID-19 PATIENTS

Asma Asghar, Salman Ali Syed, Mohammad Abdullah, Arshad Hayat, Faisal Mehmood, Khalid Azam Khan

Combined Military Hospital Lahore/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To assess the degree of QTc interval prolongation caused by Chloroquine (CQ) alone and with Azithromycin in COVID-19 patients.

Study Design: Cross sectional comparative study.

Place and Duration of Study: Department of Medicine, Combined Military Hospital (CMH) Lahore, from Apr 2020 to May 2020.

Methodology: Data of the patients above 15 years of age who were confirmed COVID-19 cases and were prescribed chloroquine alone or in combination with Azithromycin were included. Baseline electrocardiograms (ECG) and ECGs recorded 48 hours after treatment initiation were collected. Retrospective analysis of ECGs (baseline and at 48 hours) was done. Patients were stratified into two groups: one on CQ alone, other on CQ and Azithromycin. Manual measurements of the QT interval were taken and QTc was calculated for each ECG. Baseline and follow up QTc intervals were compared using paired sample t-test. A QT prolongation of more than 20 milliseconds (msec) was considered significant.

Results: A total of 90 patients aged 15 and above were included in the study. The mean QTc in the CQ group raised from 411.2 ± 20.65 msec to 438.91 ± 20.43 msec with a mean difference of 27.23 msec and *p*-value of 0.001, which was a significant prolongation. In the CQ + Azithromycin group the mean QTc increased by 407.41 ± 21.17 msec to 440.85 ± 23.11 msec with a mean difference of 33.43 msec and *p*-value of 0.001. However no significant arrhythmia was observed in any patient.

Conclusion: Chloroquine alone as well as the combination chloroquine with Azithromycin causes significant QTc prolongation.

Keywords: Azithromycin, Chloroquine, Electrocardiogram, QTc interval.

INTRODUCTION

Nearing the end of 2019, a novel Coronavirus, now known as SARS-CoV-2 (2019), made its appearance in Wuhan, China and caused havoc with major health and economic implications. As efforts are underway to combat the SARS-CoV-2 pandemic globally, Chloroquine (CQ) and Azithromycin have made their appearance as newly recommended therapeutic options. This is possibly due to the unique ability of CQ to inhibit nucleic acid amplification as well as inhibiting fusion of the virus to the cell membrane by modulating endosomal pH[1]. On the other hand, azithromycin is well recognised to have both immune modulating and antiviral properties[2]. However, equally important to the study of their role in the emerging regime is to study the side effect profile of these drugs. One sought after would be the effect they may have on corrected QT interval (QTc).

QT Interval is defined as the time calculated from the start of the Q wave to the completion of the T wave, and parallels the time taken from when the cardiac ventricles begin contraction to the end of relaxation. The contraction is brought about by the summation of action potential of ventricular muscle cells which takes places by movement of different ions across cell membrane via protein channels. Any abnormality of these channels can lead to either exaggerated inward flow or decreased outward flow leading to prolongation of the QT interval, which can eventually lead to sudden arrhythmias and potential

Correspondence: Dr Asma Asghar, Department of Medicine, CMH Lahore Pakistan (*Email: asghar.asma79@gmail.com)*

Received: 15 Jun 2020; revised received: 20 Jul 2020; accepted: 28 Jul 2020

fatal outcome. Based on the electrocardiogram (ECG) findings a QT interval prolongation is defined as a QTc of more than 450 milliseconds in males and more than 470 milliseconds in females[3].

There are 3 types of channels associated with QT Prolongation - Na, IKr and IKs. The inward potassium rectifier (IKr) also known as human ether-a-go-go-related gene (hERG) channels conduct a rapid delayed rectifier potassium current responsible for phase 3 of action potential[4]. The unique structure of hERG channel makes it prone to be affected by various drugs. Other mechanisms involved in QT prolongations are disruption of hERG channel causing loss of potassium channels, rescue of Na channels causing inward sodium current and increase in inward calcium current[5,6].

CQ belongs to a group of drugs known as 4-aminoquinolines and was has primarily been used as an antimalarial drug. It causes increase in the pH of intracellular organelles such as endosomes and lysosomes mandatory for membrane fusion[7,8]. Its antiviral property is attributed to its influence on virus-receptor binding. The mechanism is thought to be its ability to interfere with terminal glycosylation of the cellular receptor, angiotensin-converting enzyme-2[9]. It also causes blockage of the rapidly activating delayed rectifier K+ current, encoded by the human ether-a-go-go-related gene (hERG) which ends up in prolongation of the action potential duration. As a result QT interval of the electrocardiogram (ECG) lengthens leading to fatal polymorphic ventricular tachyarrhythmia also known as Torsade de Pointes (TdP).

Azithromycin is an antibiotic of macrolide group. Macrolides are protein synthesis inhibitors. Azithromycin although considered relatively safe but can cause QT interval prolongation especially in older age group[10]. A major concern when prescribing chloroquine with azithromycin is the risk of QTc prolongation. So far, no data is available on the potential of these drugs causing QTc prolongation in COVID-19 patients. The objective of our study was to assess the degree of QT prolongation, if any, caused by these treating drugs.

METHODOLOGY

This was a cross sectional comparative study. It was conducted in Combined Military Hospital (CMH) Lahore. The study was conducted from 1st April 2020 to 30th May 2020. The approval was taken from the Ethical Review Committee (IRB number188/2020). All patients enrolled were aged 15 years or older hospitalized with confirmed COVID-19 disease proven by the Reverse Transcriptase Polymerase Chain Reaction (RT-PCR). PCR was done by Genesig by Primer design UK. Record of patients who had bradycardia in baseline ECG and were known cases of advanced renal or liver disease, ischemic heart disease, bradyarrhythmia, and cardiomyopathy or were on drugs causing bradycardia was excluded. ECGs of the patients who had abnormalities in baseline or follow up electrolytes, like hyper or hypokalaemia or hyper or hypomagnesemia were also excluded. Furthermore, hospital records and history charts were retrospectively searched to look for any other potential drugs that can cause QT prolongation and such patients were also excluded from the study.

Patients were then stratified into two groups – group A on CQ alone, B on CQ and Azithromycin. CQ was given 600mg twice daily and azithromycin 500mg once daily. For both groups, the baseline electrocardiogram (ECG) done at admission and ECGs recorded during treatment were collected. The ECGs were recorded using a standard machine which was calibrated prior to measurement. ECG was recorded using standard 12 leads with speed of machine at 25mm/sec with a deflection of 10mm representing 1mV on ECG paper. QT interval was measured manually on the ECG strip taken from Limb Lead II as they have the greatest positive and negative predictive value in detecting abnormal QT interval[11]. The formula employed to calculate the QTc is the Bazett Formula (table-I). A mean value was

derived from at least 3 cardiac cycles at each recording.

After a baseline recording at admission, as per standard hospital policy, 48 hours later a second ECG was checked and a second mean QTc (QT2) was calculated and both means were compared. A QT prolongation of more than 20 milliseconds (msec) was considered significant[12].

Data was analysed using SPSS version 26. The paired samples t-test was used to detect the difference of means between QTc1 (baseline) and QTc2 (48 hour after initiation of treatment) in patients using chloroquine alone and in patients given chloroquine with azithromycin. A *p*-value <0.05 was considered statistically significant.

RESULTS

A total of 90 confirmed COVID-19 patients were observed during the study period. Patients aged 15 to 74 years were studied (mean age 43.4). Amongst the 90 patients 71 (78.9%) were males and 19 (21.1%) were females. After diagnosis of COVID-19 was confirmed based on the PCR positivity, a baseline ECG was done and the QTc was measured followed by another measurement taken 48 hours later. A difference in both the QTc intervals i.e., baseline and recorded at 48 hours of treatment was calculated and student t test was applied to see for a significant impact. All the patients received CQ and almost 46 (50%) received both CQ and Azithromycin.

Table-I: Methods to correct QT interval for heart rates.

Correction	Formula to Calculate QTc
Bazett	QTc = QT/√RR
Fredericia	QTc = QT/(RR) 1/3
Framingham	QTc = QT + 0.154 (1 – RR)

The mean QTc in the CQ group rose from 411.68 ± 20.65 msec to 438.91 ± 20.43 msec with mean difference of 27.23 msec and *p*-value of 0.001, which was a significant lengthening of the QT interval. This shows that CQ therapy significantly prolongs the QT interval. Similarly, in the CQ + Azithromycin group the mean QTc increased from 407.41 ± 21.17 msec to 440.85 ± 23.11 msec with a mean difference of 33.43 msec and *p*-value of 0.001, which too was a significant lengthening. It is clearly evident that the group treated with both the drugs had a more significant prolongation of the QT interval compared with the one treated with chloroquine alone. Nonetheless, none of the patients developed any arrhythmias throughout the treatment period, as serial ECGs were studied.

DISCUSSION

The aim of conducting this study was to identify a potentially lethal side effect, QT interval prolongation, that may occur as a result of the drugs such as CQ and Azithromycin used in the trial regimen for the COVID-19 patients. Results of our study clearly demonstrate a prolongation of QT interval due to chloroquine alone as well as with azithromycin. There is also more pronounced prolongation due to combination as compared to chloroquine alone. These results are consistent with the findings of a multicentre study done at 3 hospitals of the New York State Northwell Health system by Moussa *et al*. Study was carried out on 201 patients who were on either CQ or hydroxychloroquine alone or in combination

Table–II: Illustrating the effect of CQ alone on Mean QTc.

CQ	n	Mean ± SD	Mean Difference	95% Confidence Interval		*p*-value
				Lower	Upper	
QTc1 (Baseline)	44	411.68 ± 20.65	27.23	405.40	417.96	0.001
QTc2 (at 48 hours)	44	438.91 ± 20.43		432.70	445.12	

Table-III: Illustrating the effect of CQ + Azithromycin on Mean QTc.

CQ + Azithromycin	n	Mean ± SD	Mean Difference	95% Confidence Interval		*p*-value
				Lower	Upper	
QTc1(baseline)	46	407.41 ± 21.17	33.43	401.14	413.70	0.001
QTc2(at 48 hours	46	440.85 ± 23.11		433.99	447.71	

with azithromycin[13]. Baseline QTc intervals were compared with the maximum QTc during treatment. Baseline QTc intervals was found to be the same when compared in patients treated with chloroquine/hydroxychloroquine (monotherapy group) and the one treated with the drug combination (440.6 ± 24.9 ms vs. 439.9 ± 24.7 ms, p=0.834). The maximum QTc during treatment was significantly lengthened in the group on drug combination regimen as compared to the group on single drug (470.4 ± 45.0 ms vs. 453.3 ± 37.0 ms, p=0.004). They also had to stop treatment for 3.5% patients due to prolonged QTc[13]. However, no fatal arrhythmia was noted which is quite similar to our study.

Some review based studies have also emphasized the importance of performing baseline ECGs for patients being planned to be treated with the drugs notorious for their potential for QTc interval prolongation. Exaggerated prolongation of the QT interval many be caused by many drugs used in cardiology setting as well as those used in the treatment of multiple other conditions[14]. While a number of trials of different drugs are underway for the potential treatment of this novel disease, it is all the more essen-tial to promptly diagnose drug-induced QT prolongation. A recent review from Mayo Clinic has highlighted the importance of adopting a proper mechanism or protocol to avoid development of arrhythmias during pandemic of COVID-19. According to the review a cuff value of QTc intervals 470 msec in males and 480 msec in females should raise the possible risk for ventricular arrhythmias whereas QTc intervals greater than 500 ms should be taken as a risk factor for torsade de pointes[14]. Another article by the Mayo Clinic has even proposed a protocol for QTc monitoring[15].

Azithromycin has been studied with a view to its impact on QTc interval. This effect has been found predominantly studied in elderly population, but its effects in young people have not been studied extensively. Data on CQ is pretty scarce as well. Our study provides an insight into both these research gaps. A study on vast number of patients' electronic record in a tertiary care hospital in Korea revealed that the chance of QT prolongation was most pronounced in patients taking azithromycin in age bracket of 60 to 79 years[10]. There are studies from other parts of world in support of same observation[16,17]. The most feared consequence associated with QT interval prolongation is Torsade de Pointes (TdP), a fatal arrhythmia which does not give the physician much time for apt management. There is a long list of medication that can lead to TdP including anti malarials and macrolides however no such arrhythmia was found in any patient in our study[18].

There are numerous factors which can potentiate the effect of these drugs on QT interval including advanced age, electrolyte imbalance, pre-existing bradyarrhythmia, concomitant use of diuretics female gender, cardiac ischemia with compromised ejection fraction[19]. Literature review reveals a study showing the possibility of chloroquine induced cardiomyopathy[20]. Our study does not include the echocardiograms of the patients therefore impact of these drugs on cardiac function cannot be assessed. However it was not the objective of this study as well.

Although many different methods have been suggested for correcting QT intervals for heart rate, yet each method has its own positive and negative aspects. There is no agreement on which of these to be adopted. However, the most commonly used is Bazett's formula ($QTc = QT/\sqrt{RR}$ in seconds) that corrects the QT interval quite reliably for heart rate ranging from 60 to 100 beats/min. Still there remains a chance of underestimation and overestimation of the QT interval at low and high heart rates, respectively.

This study has certain limitations. Firstly, the study was carried out in a single tertiary care, teaching hospital. Validation by conducting the study in other clinical care settings would add strength to the concept of clinical prediction of QT interval prolongation with the use of CQ and Azithromycin. It is also true that there is an inevitable limitation associated with measurement of

QT intervals from 12-lead ECGs and ECG rhythm strips, as measurements performed have a performer-bias and can often be incorrect. Despite this, we tried to eliminate such bias by taking at least 3 readings at each recording and used mean values for all QT interval values.

CONCLUSION

Chloroquine alone as well as the combination of chloroquine and azithromycin cause significant prolongation of QT interval. This effect is more pronounced when the two drugs are used together compared to chloroquine alone. Therefore caution needs to be exercised while prescribing them and vigilant ECG monitoring should be carried out for all the patients using them. The essential role of these Interval prolongation analysis on overall patient safety outcomes, such as TdP and sudden cardiac death can ultimately reduce the health care costs and more importantly, the health care burden as the struggle to find a suitable regimen for the COVID-19 pandemic continues.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Gendrot M, Javelle E, Clerc A, Savini H, Pradines B. Chloroquine as a prophylactic agent against COVID-19? Int J Antimicrob Agents 2020; 55(6): 105980.
2. Pani A, Lauriola M, Romandini A, Scaglione F. Macrolides and viral infections: focus on azithromycin in COVID-19 pathology. Int J Antimicrob Agents 2020; 106053.
3. Goldenberg I, Moss AJ, Zareba W. QT interval: How to measure it and what is "normal." J Cardiovasc Electrophysiol. 2006; 17(3): 333-36.
4. Bartos DC, Grandi E, Ripplinger CM. Ion Channels in the Heart. Compr Physiol 2015; 5(3): 1423-1464.
5. Kuryshev YA, Ficker E, Wang L, Hawryluk P, Dennis AT, Wible BA, et al. Pentamidine-induced long QT syndrome and block of hERG trafficking. J Pharmacol Exp Ther 2005; 312(1): 316–23.
6. Ficker E, Kuryshev YA, Dennis AT, Obejero-Paz C, Wang L, Hawryluk P, et al. Mechanisms of arsenic-induced prolongation of cardiac repolarization. Mol Pharmacol 2004; 66(1): 33–44.
7. Martínez A, Rajapakse CSK, Naoulou B, Kopkalli Y, Davenport L, Sánchez-Delgado RA. The mechanism of antimalarial action of the ruthenium(II)-chloroquine complex [RuCl2(CQ)]2. J Biol Inorg Chem 2008; 13(5): 703–12.
8. Foley M, Tilley L. Quinoline antimalarials: mechanisms of action and resistance. Int J Parasitol 1997; 27(2): 231-40.
9. Smit C, Peeters MYM, van den Anker JN, Knibbe CAJ. Chloroquine for SARS-CoV-2: Implications of Its unique pharmacokinetic and safety properties. Clin Pharmacokinet 2020; 0123456789.
10. Choi Y, Lim HS, Chung D, Choi J, Yoon D. Risk Evaluation of Azithromycin-Induced QT Prolongation in Real-World Practice. Biomed Res Int 2018; 2018: 1-8.
11. Mönnig G, Eckardt L, Wedekind H, Haverkamp W, Gerss J, Milberg P et al. Electrocardiographic risk stratification in families with congenital long QT syndrome. Eur Heart J 2006; 27(17): 2074-80.
12. Nachimuthu S, Assar MD, Schussler JM. Drug-induced QT interval prolongation: mechanisms and clinical management. Ther Adv Drug Saf 2012; 3(5): 241-53.
13. Saleh M, Gabriels J, Chang D, Soo Kim B, Mansoor A, Mahmood E, et al. Effect of chloroquine, hydroxychloroquine, and azithromycin on the corrected QT interval in patients With SARS-CoV-2 Infection. Circ Arrhythm Electrophysiol 2020; 13(6): 008662.
14. Roden DM. Predicting drug-induced QT prolongation and torsades de pointes. J Physiol 2016; 594(9): 2459–68.
15. Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the qtc-prolonging and torsadogenic potential of possible pharmacotherapies for coronavirus disease 19 (COVID-19). Mayo Clin Proc 2020; 95(6): 1213.
16. van den Broek MPH, Möhlmann JE, Abeln BGS, Liebregts M, van Dijk VF, van de Garde EMW. Chloroquine-induced QTc prolongation in COVID-19 patients. Netherlands Hear J 2020; 1(1): 1-4.
17. Sears SP, Getz TW, Austin CO, Palmer WC, Boyd EA, Stancampiano FF. Incidence of sustained ventricular tachycardia in patients with prolonged QTc after the administration of azithromycin: A retrospective study. Drugs Real World Outcomes 2016; 3(1): 99-105.
18. Ohara H, Nakamura Y, Watanabe Y, Cao X, Yamazaki Y, Izumi-Nakaseko H, et al. Azithromycin can prolong qt interval and suppress ventricular contraction, but will not induce torsade de pointes. Cardiovasc Toxicol 2015; 15(3): 232–40.
19. Tisdale JE. Drug-induced QT interval prolongation and torsades de pointes: Role of the pharmacist in risk assessment, prevention and management. Can Pharm J (Ott) 2016; 149(3): 139-52.
20. Yogasundaram H, Hung W, Paterson ID, Sergi C, Oudit GY. Chloroquine-induced cardiomyopathy: a reversible cause of heart failure. ESC Hear Fail 2018; 5(3): 372-75.