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The effect of 5-day course of hydroxychloroquine and azithromycin combination on QT interval in non-ICU COVID19(+) patients

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A R T I C L E   I N F O

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A B S T R A C T

Background: The combination of Hydroxychloroquine (HCQ) and azithromycin showed effectiveness as a treatment for COVID-19 and is being used widely all around the world. Despite that those drugs are known to cause prolonged QT interval individually there is no study assessing the impact of this combination on electrocardiography (ECG). This study aimed to assess the impact of a 5-day course of HCQ and azithromycin combination on ECG in non-ICU COVID19(+) patients.

Methods: In this retrospective observational study, we enrolled 109 COVID19(+) patients who required non-ICU hospitalization. All patients received 5-day protocol of HCQ and azithromycin combination. On-treatment ECGs were repeated 3-6 h after the second HCQ loading dose and 48-72 h after the first dose of the combination. ECGs were assessed in terms of rhythm, PR interval, QRS duration, QT and QTc intervals. Baseline and on-treatment ECG findings were compared. Demographic characteristics, laboratory results were recorded. Daily phone call-visit or bed-side visit were performed by attending physician.

Results: Of the 109 patients included in the study, the mean age was 57.3 ± 14.4 years and 48 (44%) were male. Mean baseline PR interval was 158.47 ± 25.10 ms, QRS duration was 94.00 ± 20.55 ms, QTc interval was 435.28 ± 32.78 ms, 415.67 ± 28.51, 412.07 ± 25.65 according to Bazett’s, Fridericia’s and Framingham Heart Study formulas respectively. ΔPR was −2.94 ± 19.93 ms (p = .55), ΔQRS duration was 5.18 ± 8.94 ms (p = .03), ΔQTc interval was 6.64 ± 9.60 ms (p = .5), 10.67 ± 9.9 ms (p = .19), 14.14 ± 9.68 ms (p = .16) according to Bazett’s, Fridericia’s and Framingham Heart Study formulas respectively. There were no statistically significant differences between QTc intervals. No ventricular tachycardia, ventricular fibrillation or significant conduction delay was seen during follow-up. There was no death or worsening heart function.

Conclusion: The 5-day course of HCQ-AZM combination did not lead to clinically significant QT prolongation and other conduction delays compared to baseline ECG in non-ICU COVID19(+) patients.

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Introduction

Since reporting of the first case on December 9 in Wuhan, China, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread swiftly in a short time throughout China and the outside [1]. In early March World Health Organization (WHO) declared the SARS-CoV-2 outbreak a pandemic [2]. Due to the lack of specific antiviral medication for treatment and vaccine for prevention “repurposing” drugs emerged as a rescuer to deal with this problem. Several known molecules were started to be tested in different countries [3–5]. Hydroxychloroquine is an analogue of chloroquine and has been used as an antimalarial and antirheumatic drug [6]. Antiviral effects of HCQ had been demonstrated [7,8]. In a recent study HCQ reinforced by azithromycin was associated significantly with viral load reduction in COVID19 (+) patients [3].

Chronic HCQ use demonstrated QT prolongation and refractory ventricular arrhythmia [9], and azithromycin has been reported to be related to QT prolongation, sudden cardiac arrest, and increased cardiac mortality [10,11]. Since HCQ is metabolized by cytochrome P450 enzymes and azithromycin inhibits this enzyme [12,13], this adverse effect brings about safety issues. Despite HCQ - AZM combination was found...
effective and well tolerable in the treatment of COVID19 there is no study assessing the impact of this combination on ECG [14]. In this study, we aimed to evaluate the ECG changes in COVID19(+) patients taking HCQ–AZM combination.

Methods

Study population

Our study was designed as a retrospective observational study. We screened the records of 196 COVID19(+) patients presented to our hospital between March 31 and April 16 and who were followed in outpatient wards and received HCQ –AZM combination therapy. Pregnancy, patients under 18 years and patients who did not have control ECG were exclusion criteria. After exclusion, we included 109 patients in the study. The flowchart was described in Fig. 1. Patients who had COVID19(+) with asymptomatic or mildly symptomatic (such as the upper respiratory infection) and without comorbidity followed in the outpatient clinic and excluded from the study. Patients with the lower respiratory infection (such as pneumonia or bronchitis), 1 and more comorbidity and age more than 64 years were hospitalized to inpatient ward if SpO2 is more than 98% and hemodynamically stable.

Baseline and control ECG were obtained. Control ECGs were repeated 3–6 h after the second HCQ loading dose and 48–72 h after the first dose of the combination. ECGs were assessed in terms of rhythm, PR interval, QRS duration, QT and QTc intervals. Baseline and control ECG findings were compared. Demographic characteristics, laboratory results were recorded. Daily phone call-visit or bed-side visit were performed by attending physician.

Treatment protocol

The treatment protocol was adopted by the national health system and sent to all centers. According to this protocol, most patients after diagnosing COVID19(+) were started Hydroxychloroquine if not any contraindication. Azithromycin was given if there is concomitant pneumonia. Oseltamivir was the part of the protocol until in cardiologist (NB). In case of problems with measurement, the second cardiologist (AE) measured blindly the QT interval to the first cardiologist. If discrepancy between these two cardiology was more than 0.05, the third cardiologist (EK) were invited to resolve the problem. The PR interval was described the interval measured from the onset of the P wave to the beginning of the first point of deflection of the QRS complex. The QRS duration was the interval between the first deflection of the QRS complex and the returning point to the baseline. The QT interval was measured from the onset of the first deflection of QRS complex to the end of T wave. The end of the T wave was determined by the tangent method. QT measurement was performed according to guideline proposed by expert panel [15]. The corrected QT (QTc) interval was calculated by the Bazett’s, Fridericia’s and Sagie’s (Framingham Heart Study) formulas. All measurements were performed manually in EP calipers software (EP Studios, Inc., Version 3.1).

Statistical analysis

Continuous variables were expressed as mean standard deviation, categorical variables were expressed as median with interquartile range. The data was tested by the Kolmogorov – Smirnov test or Shapiro– Wilk test and a visual inspection of histograms for homogeneity. Changes in the baseline, after loading and during maintaining dose were analyzed by Friedman test or repeated measure ANOVA where appropriate. Normally distributed continuous variables were expressed as mean ± standard deviation, non-parametric continuous variables were expressed as median with interquartile range, while percentiles were used for categorical variables. \( p < .05 \) was considered as statistically significant. Statistical analyses were performed using SPSS version 22.0 (IBM Inc. USA).

Results

A total of 109 patients eligible for analysis fulfilled the following inclusion criteria: 1) Patients who were in sinus rhythm; 2) Patients >18 years and were followed in in-patient ward; 3) Patients who were started HCQ and azithromycin combination; 4) Patients who had at least 2 control ECGs during the treatment period. Exclusion criteria were: 1) cardiac rhythm other than sinus; 2) Early discharged patients; 3) patients whose combination treatment was changed due to course of the disease (other than cardiac or arrhythmic reasons); 4) Pregnancy. One hundred and nine patients were included in the study. Of them,
48 (44%) were male and the mean age was 57.3 ± 14.4 years (Table 1). Compared with baseline QTc interval, QT prolongation ≥50 ms and QTc interval ≥500 ms was observed in 2 (1.8%) patients. We analyzed baseline QTc interval and ΔQTc according to serum potassium level (serum K+ < 4.0 mmol/L vs. serum K+ ≥ 4.0 mmol/L). In contrast to higher serum potassium level (K+ ≥ 4.0 mmol/L), lower serum potassium level (serum K+ < 4.0 mmol/L) were associated with statistically significantly longer QT interval. But no difference existed between ΔQTc interval in this subgroup. This may be related to potassium replacement in patients who had lower serum potassium level (serum K+ < 4.0 mmol/L). Detailed results were demonstrated in Table 5. No ventricular tachycardia, ventricular fibrillation or significant conduction delay was seen during follow-up. There was no death or worsening heart function.

Discussion

In our study, we showed that the 5-day course of HCQ-AZM combination does not cause significant QT prolongation and other conduction delays and this protocol was safe in terms of malignant cardiac arrhythmias. The changes in QTc interval (according to Bazett’s formula) was demonstrated in Fig. 2. Our results can be summarized as followings: 1) The risk for QT prolongation with this combination is not frequent. 2) The QT prolongation that was seen after loading doses of HCQ (800 mg) and AZM (500 mg) were shortened during maintenance doses. Given that this trend in the QT interval, it may be suggested that QT prolongation was the result of the acute effect of HCQ and this was dose-related. We could not find a similar outcome in the previous studies. Tett et al. reported similar results with chloroquine [16]. 3) Serum potassium level was lower who had QT prolongation >50 ms in comparison to whom QT prolongation <50 ms. 4) HCQ lowered serum potassium level and this may exacerbate hypokalemia. Hypokalemia per se with other QT-prolonging drugs can worsen myocardial repolarization.

Two potassium ion channels, delayed rectifier K+ current (Ikr (rapid) and Ik(slow)) primarily carry out myocardial repolarization. Virtually Ikr was blocked by QT-prolonging drugs [17]. Blockade produces prolongation of the action potential by delaying in phase 3. This increased duration is reflected by QT prolongation. De Bruin et al. established a clear correlation between the drug’s ability to block Ikr and its potential to induce malignant ventricular arrhythmias and sudden cardiac death [18].

Hydroxychloroquine is a chloroquine analogue. Its pharmacokinetics vary widely in different diseases. Bioavailability can range from 25 to 100%. Mean absorption half-life is about 4 h and 40% of drug binds to serum proteins (mostly to albumin). Hydroxychloroquine metabolizes in the liver and excretes from the kidney as metabolites and unchanged from [16]. Hydroxychloroquine impacts on the cell membrane and causes potassium inflow [19]. Hypokalemia following HCQ use can be interpreted by this effect [20]. During our study, we observed a prominent decrease in serum potassium level after loading dose compared to the maintenance dose. Baseline and control (after the loading dose of HCQ dose) serum potassium were 4.13 ± 1.11 mmol/L and 4.0 ± 1.03 mmol/L respectively (p = .02).

QT prolongation, QRS widening was reported as a potential adverse effect of HCQ. Profound bradycardia or advanced AV block and other serious adverse effects were rare [21]. Cardiomyopathy with azithromycin has been reported [21].

Recently conducted chloroquine (CQ) study was stopped prematurely due to increased mortality rate with high dose CQ (the cumulative dose 12 g) in comparison to low dose (the cumulative dose 2.7 g) [22]. Hydroxychloroquine is less toxic than CQ [16]. In our study, there were no significant cardiac adverse effects with HCQ and it was well tolerated. Concomitantly, 75% of patients received oseltamivir and 8% favipiravir.
Azithromycin is a macrolide. Oral bioavailability is low and affected by foods. After taken 500 mg azithromycin orally it takes 2 h to reach serum peak concentration. Binding to plasma protein is low. Similar to other macrolides azithromycin interacts with the cytochrome P-450 enzymes partly and this rises concern about drug interaction when used together. There were no significant interactions before in clinical practice [24]. In our study, there was no significant QT prolongation despite at least 68% of patients received three QT-prolonging medications. Along with HCQ/AZM, 7 (6.4%) patients were received SSRI, 1 (0.9%) patient received amiodarone and 1 (0.9%) patient received ranolazine. No difference was observed on ECGs of these patients compared to other patients.

Azithromycin is known as the safest macrolide in terms of cardiac events [25], this can be derived from unique monophagic action potential configuration compared with clarithromycin and erythromycin. But conflicting studies exist regarding the cardiovascular safety of azithromycin [26]. The QT prolongation and proarrhythmic effects that were reported previously were induced by azithromycin [10,27–29]. Ray et al. reported the increased cardiovascular mortality rate especially in patients who had cardiovascular risk factors with the 5–day course of azithromycin in comparison to amoxicillin [11]. However, Mortensen et al. determined that in comparison to other antibiotics azithromycin was safe and did not increase cardiac arrhythmias and heart failure among older population [30]. In Danish adult cohort study, azithromycin was not associated with increased cardiovascular risk as compared with penicillin V in young and middle-aged adults [31].

There are some limitations to our study. The sample size was small and designed as a single center study. We could not compare our outcomes with other protocols. The QT interval can be affected by several factors including medications, metabolic status, hypoxia, ischemia and underlying pathologies. Patients who were followed in the intensive care unit and who was intubated can be susceptible to QT-prolonging medications. Hence our results should not be generalized to all patients who are a candidate for HCQ and azithromycin combination. We did not perform a power analysis to calculate sample size that we need to predict the prevalence of significant QT prolongation following HCQ and azithromycin combination. However, our study demonstrated that prolonged QT interval after HCQ and azithromycin loading dose

### Table 3

| Parameters | Δ1 (on-treatment ECG vs. baseline ECG) | P value | Δ2 (on-treatment vs. Δ1, on-treatment ECG) | P value | Δ2 (on-treatment ECG vs. baseline ECG) | P value |
|------------|--------------------------------------|---------|------------------------------------------|---------|--------------------------------------|---------|
| Heart rate, bpm, mean ± SD | 10 ± 1 | < 0.001 | 1 ± 1 | 0.4 | 10 ± 1 | < 0.001 |
| RR duration, ms, mean ± SD | 62.53 ± 9.42 | < 0.001 | 14.47 ± 14.17 | 0.29 | 77 ± 24.95 | 0.009 |
| PR interval, ms, mean ± SD | -2.12 ± 18.90 | 0.65 | -0.82 ± 9.79 | 0.73 | -2.94 ± 19.93 | 0.55 |
| QRS duration, ms, mean ± SEM | 3.88 ± 8.37 | 0.074 | 1.29 ± 8.51 | 0.54 | 5.18 ± 8.94 | 0.03 |

### Table 4

**Comparison of electrocardiographic findings during treatment course.**

### Table 5

**Comparison of mean baseline QTc and ΔQTc interval according to baseline serum potassium level.**

| Parameters | ΔQTc and ΔQTc, ms, Mean ± SD | N = 42 | Serum K⁺ < 4.0 mmol/L | Serum K⁺ ≥ 4.0 mmol/L | P value |
|------------|-----------------------------|-------|-----------------------|----------------------|--------|
| QTc by Bazett | 451.46 ± 33.44 | 435.82 ± 25.50 | 0.007 |
| ΔQTc by Bazett | 8.66 ± 37.03 | 7.26 ± 26.97 | 0.82 |
| QTc by Frederic | 425.69 ± 30.64 | 410.23 ± 26.26 | 0.006 |
| ΔQTc by Frederic | 13.43 ± 39.07 | 11.41 ± 27.77 | 0.75 |
| QTc by FHS | 423.46 ± 28.28 | 409.91 ± 29.82 | 0.009 |
| ΔQTc by FHS | 13.53 ± 37.85 | 10.91 ± 25.89 | 0.67 |

FHS- Framingham Heart Study.

Bold indicates statistically significant value. *minus * - indicates shortened duration. Bold indicates statistically significant value. SE.
generally shortened during the maintenance period. By increasing the number of patients and centers attended the study, our results need to be confirmed.

Conclusion

The 5-day course of HCQ -AZM combination did not lead to significant QT prolongation and other conduction delays compared to baseline ECG in non-ICU COVID19(+) patients.

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