Short Communication

Why we should be more careful using hydroxychloroquine in influenza season during COVID-19 pandemic?

Hülya Gamze Çelik[a], Şiran Keske[b], Ülker Şener[c], Müge Tekbaş[d], Mahir Kapmaz[e], Şükrü Taylan Şahin[a], Aslı Özyıldırım[c], Saide Aytekin[f], Vedat Aytekin[f], Önder Ergönül[e,*]

[a] Department of Cardiology, American Hospital, Istanbul, Turkey
[b] Department of Infectious Diseases, American Hospital, Istanbul, Turkey
[c] Department of Pharmacy, American Hospital, Istanbul, Turkey
[d] Department of Pharmacy, Koç University Hospital, Istanbul, Turkey
[e] Koç University İş Bank Research Center for Infectious Diseases, Istanbul, Turkey
[f] Department of Cardiology, Koç University School of Medicine, Istanbul, Turkey

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ABSTRACT

The aim of this study was to describe the QTc prolongation and related adverse cardiac events during the administration of hydroxychloroquine (HCQ) and its combinations for the treatment of coronavirus disease 2019 (COVID-19). Hospitalized patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) who received HCQ and had initial and follow-up electrocardiograms performed between March 10 and May 30, 2020 were included. Critical QTc prolongation was detected in 12% of the patients. On multivariate analysis, diabetes mellitus (odds ratio 5.8, 95% confidence interval 1.11–30.32, p = 0.037) and the use of oseltamivir (odds ratio 5.3, 95% confidence interval 1.02–28, p = 0.047) were found to be associated with critical QTc prolongation.
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Introduction

One of the most commonly used first-line treatments for coronavirus disease 2019 (COVID-19) is hydroxychloroquine (HCQ) with or without azithromycin (AZT) (Yao et al., 2020). HCQ is used for autoimmune disorders such as systemic lupus erythematosus and is reported to be a safe and well-tolerated drug (Tang et al., 2012). It is also known to reduce the cardiovascular risks in rheumatoid arthritis patients (Sharma et al., 2016). On the other hand, it inhibits the voltage-gated sodium and potassium channels and prolongs repolarization (QT) of the cardiac cycle, which might increase the risk of Torsade de Pointes (TdP) and sudden cardiac arrest (Chorin et al., 2020; Jankelson et al., 2020; Meeting, 2017). The aim of this study was to describe the corrected QT (QTc) prolongation and related cardiac events associated with HCQ in patients with COVID-19.

Methods

Inpatients with probable and confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection based on the World Health Organization definitions (WHO, 2020) and who received HCQ between March 10 and May 30, 2020 in two affiliated hospitals were included in this study. COVID-19 patients who had initial and follow-up electrocardiograms (ECGs) were analysed; those patients who had neither initial nor follow-up ECG performed and those who were transferred from other centres while using HCQ were excluded. Lead II was utilized for the measurement of the QTc on ECG or on telemetry. Bazett's formula was used to calculate the corrected QTc. If the baseline QTc level was below 450 ms, ECG was re-evaluated on day 3–5 of HCQ treatment; if the QTc level was between 450 ms and 499 ms, ECG was re-evaluated daily. Critical QTc prolongation was defined as prolongation of QTc or ΔQTc levels (>500 msn and >60 msn, respectively). ΔQTc is the difference between the maximum QTc during treatment and baseline QTc (QTc max − QTc baseline). If a baseline bundle branch block (QRS > 120 ms) was present, critical prolongation of QTc was accepted as 550 ms (Helfenbein et al., 2006).

The loading dose of HCQ was 400 mg twice daily on the first day and 200 mg twice daily for the following 4 days. The loading dose
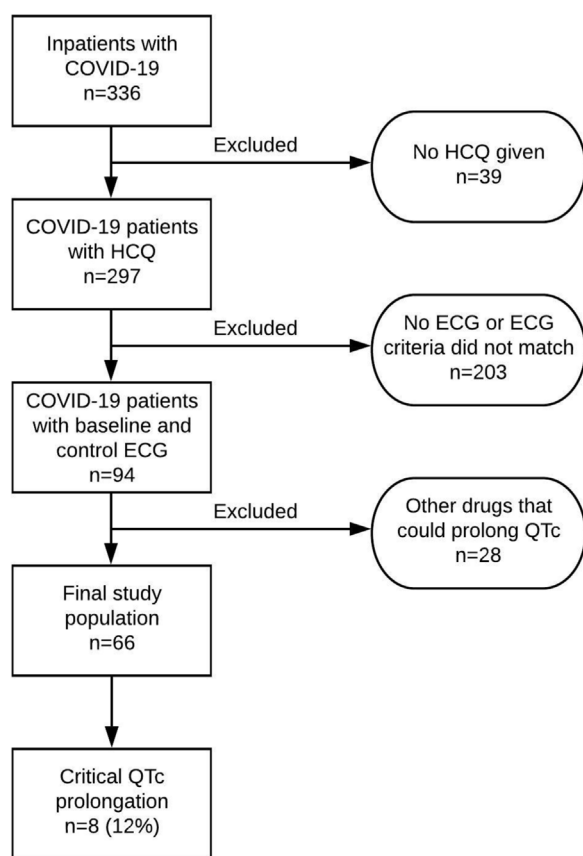
Figure 1. The study population. (HCQ: hydroxychloroquine, ECG: electrocardiogram.).

of azithromycin was 500 mg once daily on the first day and 250 mg once daily for the next 4 days. The primary outcomes were critical QTc prolongation, TdP, ventricular tachyarrhythmia, and sudden cardiac arrest.

Categorical variables were compared using the Chi-square test. For continuous variables, the non-parametric Kruskal–Wallis test was used. Stata version 16 (StataCorp, College Station, TX, USA) was used for the statistical analysis, and statistical significance was set at a p-value <0.05.

Results

HCQ was administered to 297 of 336 hospitalized patients with COVID-19; 66 of these 297 patients were included in the final

analysis (Figure 1). In total, 67% of the cases were confirmed, while 23% were probable. Characteristics of the patients are presented in Table 1. Twenty-four percent of the patients were admitted to the intensive care unit (ICU) and 6.25% died. The ICU admission rate was similar among patients who had HCQ monotherapy and those who had HCQ plus AZT: 25.0% and 23.1%, respectively ($p = 0.86$). The mortality rate was also similar in the monotherapy and combined treatment groups: 5.1% and 8.0%, respectively ($p = 0.64$). Overall, QTc levels were increased under HCQ treatment in 63% of the patients, and critical QTc prolongation occurred in eight patients (12%), all of whom were male (Table 1). The mortality rate was 42.9% among patients with QT prolongation, while it was 1.75% among patients without QT prolongation ($p < 0.001$).

On multivariate analysis, it was found that diabetes mellitus was more frequent among patients who had critical QTc prolongation (odds ratio (OR) 5.8, 95% confidence interval (CI) 1.11–30.32, $p = 0.037$). The concomitant use of oseltamivir was also more frequent in the same group (OR 5.3, 95% CI 1.02–28, $p = 0.047$) (Table 2).

Discussion

In this study, the effect of HCQ on QTc prolongation was evaluated in patients with COVID-19. Critical QTc prolongation was detected in 12% of the population, which is similar to the results of two recent studies (Ramireddy et al., 2020; Saleh et al., 2020). However, in another study, critical QTc prolongation was reported in 20% of cases (Mercuro et al., 2020). HCQ and AZT are listed as drugs that prolong the QT interval (RL et al., 2020; Zengin et al., 2020). In a recent study, the risk of QTc prolongation was found to be higher in patients taking HCQ and AZT combination when compared to HCQ monotherapy (Mercuro et al., 2020); however Rosenberg et al. reported no significantly increased risk, as was also found in the present study (Table 1) (Rosenberg et al., 2020; Saleh et al., 2020). The mortality rate of the patients with QT prolongation was higher than that of the patients without QT prolongation ($p < 0.001$). The ECGs of the fatal cases were evaluated while they were in the ICU and none of the fatal cases ended up in TdP. Therefore, QT prolongation was not related as the cause of fatality, since COVID-19-related cardiac complications such as myocarditis could not be ruled out.

The patients with diabetes mellitus had a significantly higher rate of critical QTc prolongation (OR 5.8, 95% CI 1.11–30.32, $p = 0.037$; Table 2), although the baseline QTc levels were similar ($p = 0.4$). Although pre-diabetic and newly diagnosed diabetes mellitus patients are at risk of cardiac autonomic neuropathy (CAN), those diabetic patients who have poorly controlled blood glucose levels and a longer duration of disease are at higher risk (Spallone et al., 2011; Ziegler et al., 2015).

Table 1
Comparison of the characteristics of patients with critical QTc prolongation and other patients.

	Total N = 66 (%)	Critical QTc prolongation n = 8 (%)	No critical QT prolongation n = 58 (%)	p-Value
Sex, n (%)				0.033
Male	44 (67)	8 (100)	36 (62)	
Female	22 (33)	0 (0)	22 (38)	
Age (years), mean ± SD	57.3 ± 21)	68 ± 16	56 ± 22	0.134
Hypertension, n (%)	25 (38)	4 (50)	21 (36.2)	0.451
Diabetes mellitus, n (%)	20 (30)	5 (62.5)	15 (25.8)	0.035
COPD, n (%)	2 (3)	1 (12.5)	1 (1.7)	0.096
Others, n (%)	33 (50)	5 (62.5)	28 (48.2)	0.451
Being in intensive care unit, n (%)	16 (24)	4 (50)	12 (20.6)	0.07
Concurrent drugs for COVID-19, n (%)				
Azithromycin	25 (38)	5 (62.5)	20 (34.4)	0.126
Oseltamivir	21 (32)	5 (62.5)	16 (27.5)	0.047

COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; SD, standard deviation.

Table 2
Univariate and multivariate analyses by backward selection for critical QTc prolongation (*N* = 66), lroc = 76%.

	Univariate analysis			Multivariate analysis		
	OR	CI	*p*-Value	OR	CI	*p*-Value
Age	1.03	0.98–1.07	0.145	–	–	–
Diabetes mellitus	4.7	1.01–22.45	0.048	5.8	1.11–30.32	0.037
Being in intensive care unit	3.8	0.83–17.6	0.084	–	–	–
Concurrent azithromycin	3.1	0.68–14.62	0.14	–	–	–
Concurrent oseltamivir	4.3	0.93–20.46	0.061	5.3	1.02–28	0.047

CI, confidence interval; OR, odds ratio.

Oseltamivir, which is an antiviral against influenza virus, was used in the early days of the COVID-19 pandemic because of the possibility of influenza co-infection. In the present study, it was used in more than 30% of the patients, and on multivariate analysis, oseltamivir use was found to cause critical QTc prolongation more than five times. Furthermore, it has been stated in a Cochrane systematic review that oseltamivir may cause QTc prolongation (Jefferson et al., 2014).

The major limitation of this study is the lack of a control group of patients who were not treated with HCQ. The subgroup analyses may have reached a significant result if the study population was larger.

In conclusion, in this study population, diabetes mellitus and oseltamivir use were found to increase the incidence of critical QTc prolongation, but none of the patients suffered from TdP, ventricular arrhythmia, or sudden cardiac arrest. Due to the nature of COVID-19, the use of concurrent drugs and the clinical situations that have the potential to enhance QTc should be kept in mind when prescribing HCQ, and special attention should be paid to ECG monitoring.

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Ethics

The Institutional Review Board of Koç University approved the study (reference number 2020.145.IRB1.034).

Transparency declarations

None to declare.

Conflict of interest

None.

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