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The effects and reliability of the hydroxychloroquine-azithromycin combination on the cardiac conduction system in patients with coronavirus disease 2019

Koronavirüs 2019 hastalığı olan hastalarda hidroksiklorokin-azitromisin kombinasyonunun kalp iletim sistemi üzerindeki etkileri ve güvenilirliği

Berat Uğuz [1], İsmet Zengin [1], Dursun Topal [1], Selvi Öztaş [1], Selma Kenar Tiryakioğlu [1], Mustafa Adem Yılmaztepe [1]

[1] Bursa City Hospital, Department of Cardiology, Bursa, Turkey

ORCID ID of the author(s)
BU: 0000-0002-4834-5572
İZ: 0000-0003-0758-649X
DT: 0000-0001-7053-2131
SÖ: 0000-0002-0867-3264
SKT: 0000-0003-3443-6593
MAY: 0000-0001-5328-5749

Corresponding author / Sorumlu yazar:
Selma Kenar Tiryakioğlu
Address / Adres: Bursa Şehir Hastanesi, Kardiyoloji Kliniği, 16160 Nilüfer, Bursa, Türkiye
E-mail: selmatiryaki@msn.com

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Abstract

Aim: The COVID-19 virus influenced the world since late 2019 and affected millions of people. Although there is no unambiguous evidence in the treatment of COVID-19, the combination of hydroxychloroquine and azithromycin entered the protocols globally to reduce virus replication and take advantage of its immunomodulatory effects. It has been stated that both drugs extend QTc. However, the frequency of QTc prolongation in combinational drug use, and its effect on the primary endpoint, as well as the predictive values of QTc prolongation are not clear.

Methods: A total of 135 patients who received hydroxychloroquine, azithromycin, and oseltamivir for suspected / definitive COVID-19 with viral pneumonia were examined in this single-center, retrospective study,

Results: The mean age was 55.6 (19.1) years, and 61 (45%) patients were female. According to the initial ECG values, the QTc1 value was 422.44 (35.72) ms, while the QTc2 value was 446.91 (36.71) ms (P<0.001). The ECG evaluation after medication use indicated that the number of patients with a QTc value >500 ms was 6 (4.4%). The number of patients with prolongation in QTc values >60 ms was 7 (5.1%). The frequency of prolongation in QTc was 26% in intensive care unit patients, and 2% in low-risk patients in the inpatient unit. An elevation in troponin values >14 ng/L and a low GFR are predictors for QTc prolongation. None of these patients developed malignant arrhythmia or sudden cardiac death.

Conclusion: Hydroxychloroquine and azithromycin combinations used in COVID-19 patients cause a prolongation in the QTc. The incidence of prolongation in QTc varies according to the comorbid characteristics and clinical status of the patients. Before starting hydroxychloroquine and azithromycin, the risk factors and clinical status of the patients should be well evaluated.

Keywords: COVID-19, Long QT, Arrhythmia

Öz

Amaç: COVID-19 virüsü 2019'un sonlarından bu yana tüm dünyayı ve milyonlarca insanı etkiledi. COVID-19 tedavisinde net bir kanıt olmamasına rağmen, hidroksiklorokin ve azitromisinin kombinasyonu, virüs replikasyonunu azaltmak ve immünomodülatör etkilerinden yararlanmak için dünya çapında protokollere girmiştir. Her iki ilacın ayrı ayrı kullanımlarında QTc'yi uzattığı belirtilmiştir. Bununla birlikte, kombinasyonel ilaç kullanımında QTc uzamasının sıklığı ve bunun birincil sonlanım noktası üzerindeki etkisi ve ayrıca QTc uzamasının prediktif değerleri net değildir.

Yöntemler: Çalışma tek merkezli, retrospektif bir çalışma olarak tasarlandı. Viral pnömonili şüpheli / kesin COVID-19 nedeniyle hidroksiklorokin, azitromisin ve oseltamivir alan 135 hasta incelendi.

Bulgular: Ortalama yaş 55,6 (19,1) yıldı ve 61 (%45) hasta kadındı. İlk EKG değerlerine göre QTc1 değeri 422,44 (35,72) ms, QTc2 değeri 446,91 (36,71) ms (P<0,001) bulundu. İlaç kullanımı sonrası EKG değerlendirmesi, QTc değeri >500 ms olan hasta sayısının 6 (%4,4) olduğunu gösterdi. QTc değerlerinde >60 ms uzaması olan hasta sayısı 7 (%5,1) idi. QTc'de uzama sıklığı yoğun bakım hastalarında %26 iken, yataklı servis birimindeki düşük riskli hastalarda sıklık %2 idi. Troponin değerlerinde >14 ng/L yükselme ve düşük GFR, QTc uzaması için belirleyicilerdir. Bu hastaların hiçbirinde malign bir aritmi veya ani kalp durması gelişmedi.

Sonuç: COVID-19 hastalarında kullanılan hidroksiklorokin ve azitromisin kombinasyonları QTc'de uzamaya neden olur. QTc'de uzama insidansı, hastaların komorbid özelliklerine ve klinik durumuna göre değişir. Hidroksiklorokin ve azitromisine başlamadan önce, hastaların risk faktörleri ve klinik durumu iyi değerlendirilmelidir.

Anahtar kelimeler: COVID-19, Uzun QT, Aritmi

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Introduction

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization in March 2020 [1], infecting 3,136,505 people worldwide and causing death in 221,436 as of April 28, 2020 [2]. The first confirmed case in Turkey was officially announced on March 11, 2020. As of April 28, 114,653 cases and 2992 deaths occurred in Turkey from COVID-19 [3].

Though not yet a proven treatment for COVID-19, hydroxychloroquine (an analog of chloroquine) has been used in treatment protocols; researchers predict that it reduces viral proliferation and improves patient survival rates [4]. Both analogs have long been used in prophylactic pharmacotherapy for malaria, and hydroxychloroquine is also used as an antirheumatic. Both suppress the activities of pH-dependent proteases by increasing vesicular pH, thereby reducing cytokine (e.g., Tumor necrosis factor-α and Interleukin-6) production [5]. Also, in *in vitro* studies, both analogs show effectiveness against angiotensin- converting-enzyme 2 (ACE2) receptors, which is how the culprit virus (severe acute respiratory syndrome coronavirus 2) enters target cells [6]. Therefore, both analogs are anticipated to reduce the ACE2-mediated process and might also provide beneficial immunomodulatory effects during the post-viral cytotoxic storm often observed with COVID-19. As a result, these drugs have been included in treatment protocols in many countries [4].

Azithromycin, on the other hand, is an antibacterial that belongs to the macrolide group. It has immunomodulatory and anti-inflammatory properties beyond its antibiotic properties [7-9]. A study conducted in Korea showed that the risk of lengthening the QTc interval was increased when patients started treatment with azithromycin, particularly when aged between 60 to 79 years [10].

Throughout the pandemic, our center has followed the protocols of the Republic of Turkey Ministry of Health regardless of the clinical situation. The protocol specifies a loading dose of 2x400 mg hydroxychloroquine and 1x500 mg azithromycin followed by 5 daily doses of 2x200 mg hydroxychloroquine and 1x250 mg azithromycin for maintenance. Oseltamivir, dosed at 75 mg twice daily, is added when signs of viral pneumonia require hospitalization [11]. Although some data show that both azithromycin and hydroxychloroquine prolong the QTc interval when used separately, the prevalence of this and its effects on the primary endpoint in COVID-19 are unclear when combined. It is known that combining multiple proarrhythmic drugs leads to a prolonged QTc interval but that the drug-induced risk of torsades de pointes is highly variable. Therefore, use of this drug combination is predictive of an increased QTc interval, but the prevalence of this effect is unknown. Patients with multiple comorbidities or those being treated with multiple drugs that can prolong the QTc interval are at greater risk for COVID-19 and drug-induced QTc interval lengthening. It is important, when evaluating a patient from this group, to consider that the virus can cause primary myocardial damage.

The purpose of this study was to analyze the effects on the QTc interval of HCQ-AZ when used to treat probable or confirmed COVID-19 in patients showing signs of viral pneumonia. An additional aim was to determine its effect on mortality.

Materials and methods

This study was designed as a single-center retrospective analysis of patients hospitalized in our center between 11 March 2020 and 28 April 2020 with diagnosed viral pneumonia and probable or confirmed COVID-19 treated with HCQ-AZ.

Exclusion criteria included initial QTc interval exceeding 500 milliseconds (ms), presence of acute coronary syndrome, known allergies or contraindications to the treatment drugs, and known hereditary long QT syndrome. Also excluded were patients for whom our measures of interest could not be determined from the recorded ECGs.

Patients are admitted to our intensive care unit for any one of the following: Respiratory rate of at least 30/min, dyspnea and laborious breathing accompanied by SpO_2 not reaching 90% or 70 mm Hg in room air, oxygen requirement of at least 5 L/min with a nasal cannula, lactate level exceeding 2 mmol/L, hypotension (systolic blood pressure not reaching 90 mm Hg or dropping at least 40 mm Hg from the usual, or a mean arterial pressure not reaching 65 mm Hg), signs of skin hypoperfusion, signs of organ dysfunction such as confusion, abnormal kidney or liver tests, thrombocytopenia, elevated troponin levels and arrhythmia. Intensive care was provided according to the requirements stated in the health ministry directive [11]. Those who met one or more of these criteria were considered 'critically ill.' Patients who are hemodynamically stable and do not need advanced respiratory and organ support anymore were admitted "non-critically ill" and transferred to the ward.

For all patients, ECG is recorded daily. A baseline corrected QT interval (QTc1) and the maximum corrected QT interval after treatment (QTc2) were evaluated by at least two independent cardiologists, calculated using the Bazett formula (from DII/V5 derivations). Patients were classified based on the Tisdale Scale, developed by Tisdale et al. [12] in 2013. Those scoring less than 7 were considered to have low risk, and those scoring more than 11 were considered to have high risk.

Statistical analysis

Demographic data, QT intervals and QTc intervals were examined. Measured values were described using mean (standard deviation [SD]), and SPSS 22.0 was used to perform statistical comparisons. The normality of the distributions of the groups was compared using the Kolmogorov-Smirnov test, and categorical variables were analyzed using the chi-square test. A *t* test was used to compare electrocardiographic parameters between two groups. When $P<0.05$, significance was recognized.

Results

In total, 195 patients were identified, but 60 were excluded, leaving 135 enrolled participants. Mean age was 55.6 (19.1) years (range, 19-86 years), and 61 (45%) were women. Comorbidities included hypertension (47 patients, 34.8%), Type 2 diabetes mellitus (31 patients, 23.0%), stable coronary disease (25 patients, 18%) and congestive heart failure (7 patients, 5%; Table 1).

Tisdale scores were determined, and at the time, 43 patients (32%) were critically ill. Across all patients in the intensive care unit, the Tisdale score averaged 10.2, and 19 patients (44.1%) were considered to have high risk (Tisdale score ≥11) (Table 1). Invasive mechanical ventilation was required for 18 patients (41%). Vasoactive drugs were administered to 9 patients (20%), and other treatments lengthening the QT interval were administered to 11 patients (25.5%). Diuretic treatments were administered to 13 patients (30%). Of those admitted to non-critical patients (92 patients), the average of Tisdale score was 6.5, drugs that could prolong the QTc interval were administered to 25, and diuretics were administered to 16 (Table 2).

Table 1: Patients' demographics

Demographic variable	Number of patients (n=135)	Percentage (%)
Age (y)	55.6(19.1)	19-86
Sex (female/male)	61/74	45/55
Hypertension	47	34.8
Type 2 DM	31	23
Coronary heart disease	25	18
Congestive heart failure	7	5
Chronic kidney failure	7	5
Abnormal liver function	20	14
Tisdale score <7	100	66.6
7 ≤ Tisdale score ≤ 10	16	11
Tisdale score ≥ 11	19	14
Admitted to intensive care unit	43	33
Admitted to inpatient care services	92	68

Table 2: Characteristics of critically and non-critically ill patients

	Critically ill patients (n=43)	Non-critically ill patients (n=92)	*P*-value
QTc ≥ 500 ms	5 (11.6 %)	1 (1.0%)	<0.001
ΔQTc > 60 ms	6(13.9 %)	1 (1.0%)	<0.01
Need to mechanical ventilation	18	0	<0.001
Tisdale score ≥11	19 (44%)	0 (0%)	<0.001
Need to vasopressure support	9 (20%)	0	<0.001
Using QTc-prolonging drugs	11 (25%)	20 (21%)	>0.05
Diuretics usage	13 (30%)	9(10%)	<0.05
Serum potassium <3.5 mEq at QTc peak	4(9.3%)	7 (7.6%)	>0.05
Age ≥68	25(58 %)	15(16%)	<0.05
Female	14 (33%)	35 (38%)	>0.05
Baseline QTc≥460 ms	15 (35%)	7(8%)	<0.05
Comorbid disorders	13 (30%)	5 (5%)	<0.05

QTc1: baseline QTc interval, QTc2: maximum corrected, QTc: interval after treatment, ΔQT: change in corrected QT interval

Mean (SD) QTc1 was 422.44 (35.72) milliseconds (ms) and mean QTc2 was 446.91(36.71) milliseconds (ms) (P<0.001). According to baseline values, the number of patients with QTc <460 ms was 113 (83.7 %), while the number of patients with QTc ≥460 ms was 22(16.3 %). After HCQ-AZ use, ECGs showed that QTc exceeded 500 ms for 6 patients (4.4%) and was lengthened by more than 60 ms for 7 patients (5.1 %). Of those with QTc exceeding 500 ms, 5 were monitored in the intensive care unit and 1 in the inpatient unit. Of those with QTc interval lengthening by more than 60 ms, 6 (13.9 %) were monitored in the intensive care unit and 1(1.0%) in the inpatient unit. QTc prolongation was observed in 26% of the patients admitted to intensive care unit, whereas QT interval was prolonged in only 2% of the patients in non-critical group of patients. Pathological QTc prolongation rate was 9.6 % among all patients. The initial QTc values of the patients admitted to the intensive care were longer than those of non-critical ill patients (455.5 (32.7) vs. 404.0 (23.6), P<0.001).

Pathological QTc interval lengthening occurred in 11 of 22 patients (50.0 %) with QTc intervals exceeding 460 ms. On the other hand, this occurred in 2 of the 113 patients (1.7%) not in this group. The difference is significant (P<0.05).

Of the 43 people thought to be critically ill and admitted to the intensive care unit, 11 had pathological QTc prolongation. Tisdale scores of all critical patients were 10.2, while Tisdale scores of patients with prolonged QTc intervals were 9.7 on average. The Tisdale score of 2 non-critical patients was 7 on average. Diuretic drug use, comorbid disorders, and baseline QTc ≥460 msn were significantly higher in intensive care patients. There was no significant difference in electrolyte values of both groups.

Even though mean (SD) QTc intervals did not initially differ between patients with troponin levels exceeding 14 ng/L [428.4 (36.7) ms] compared to all others [426.3 (31.5) ms, P<0.05], the difference was significant after treatment [448.4 (48.0) ms vs. 421.2 (35.9) ms; P=0.001], showing QTc interval lengthening. Similarly, no difference was seen between patients with low Glomerular Filtration Rates (GFR) compared to those with normal GFRs [431.0 (39.4) vs. 418.0 (30.8) ms; $P<0.05$], but after drug therapy was initiated, the increase was remarkable between those with GFRs not reaching 60 mL/min [445.4 (46.1) ms] vs. all others [421.2 (33.5) ms; P=0.006]. Differences based on liver enzyme levels did not differ before or after drug therapy [426.9 (37.9) vs. 419.8 (35.4) ms; P>0.05 before drug therapy and 448.1 (52.2) vs. 427.7 (40.8) ms; P>0.05 after]. Troponin levels exceeding 14 ng/L and GFRs less than 60 mL/min predict pathological prolongation of the QTc interval, and liver dysfunction does not (Table 3).

Table 3: Factors associated with pathological QTc interval lengthening

	Troponin > 14 ng/L n = 45	Troponin < 14 ng/L n = 90	*P*-value
QTc1(ms)	428.4(36.7)	426.3(31.5)	>0.05
QTc2(ms)	448.4 (48.0)	429.2 (35.9)	0.001
	GFR < 60 mL/min n = 33	GFR > 60 mL/min n= 102	
QTc1(ms)	431.0 (39.4)	418.0 (30.8)	>0.05
QTc2 (ms)	445.4 (46.1)	421.2 (33.5)	0.006
	AST, ALT↑; n = 47	AST, ALT↓; n = 88	
QTc1 (ms)	426.9 (37.9)	419.8 (35.4)	>0.05
QTc2 (ms)	448.1 (52.2)	427.7 (40.8)	>0.05

QTc1: baseline QTc interval, QTc2: maximum corrected QTc interval after treatment, GFR: glomerular filtration rate, ALT: alanine transaminase, AST: aspartate transaminase, AST, ALT↑, twice the normal value, NS: not significant

Pathological QTc interval lengthening and malignant arrhythmias were not detected in any patients who died at the primary endpoint. These patients were lost based on respiratory failure. Lengthening of the QTc interval does not predict death. Lengthening was progressive, increasing to a peak on the second or third days.

Discussion

Both HCQ and AZ are drugs that can prolong QT interval, and concomitant usage increases the risk. Case reports document that hydroxychloroquine and chloroquine can prolong the QTc interval, particularly with long-term use [7], yet the World Health Organization has not issued a warning about this effect even though these drugs are commonly used as long-term antirheumatics [8].

Unlike the protocols applied in other countries, oseltamivir was part of the treatment plan in our patient population. By itself, oseltamivir at any dose was shown to provide no distinct change in the electrocardiograms (ECGs) of more than 300 volunteers; it did not affect the PR, QRS or QT intervals and did not cause pathological lengthening of QTc intervals (instead, it might have shortened the interval) [13]. That study went on to evaluate the effect of a combined hydroxychloroquine / azithromycin (HCQ-AZ) treatment.

In the present study, the incidence of QTc prolongation was 9.6%. Approximately 85% of the patients with pathological QTc prolongation were those hospitalized and monitored in the intensive care unit. QTc prolongation was observed in 26% of the patients admitted to intensive care unit, whereas QT interval was prolonged in only 2% of the patients in non-critical group of patients. In intensive care patients, QT prolongation depends on several factors including diuretic usage, comorbidities such as renal failure and baseline Qtc >460msn. Furthermore, these patients were older, had more comorbidities and septic complications and were using multiple drugs. These findings demonstrated that the occurrence of QTc interval lengthening due to the use of HCQ-AZ depends on the underlying clinical condition of the patient. When multiple drug therapies and multiple comorbidities intervene and when the patient is admitted to receive critical intensive care, the risk for QT interval prolongation is high. On the other hand, HCQ-AZ is safely used in patients who are clinically stable.

The frequency of lengthened QTc intervals was greater among those monitored in the intensive care unit compared to those given inpatient care, suggesting that this group of patients should be evaluated using a unique algorithm. Frequency of follow-up can be reduced when a patient has good clinical status, a normal troponin level, a normal GFR and a basal ECG showing a QTc interval that is less than 460 milliseconds. In intensive care patients, torsades de pointes did not occur, given that prolongation of the QTc interval is common, and monitoring should be vigilant. Remarkably, the Tisdale scores for those with prolonged QTc intervals were lower than those for patients in the intensive care unit. In this group of patients, troponin levels and GFRs should be considered along with the Tisdale score to increase reliability.

Our striking finding was that QTc interval lengthening is associated with low GFRs and elevated troponin levels. In patients with moderate renal impairment (GFR not reaching 60 ml/min), lengthening of the QTc interval might be associated with hydroxychloroquine removal from the kidney. In this study, patients with acute myocardial infarction were excluded based on an assumption that they could significantly affect mean values for the QTc interval. However, we found that some participants had elevated troponin levels. This was found to be type 2 myocardial damage or myocarditis. One limitation of this study is that these two are indistinguishable. However, in practice, a more careful evaluation of the QTc interval would be useful for patients with high troponin levels and for those who began drug therapy after being assessed in the clinic.

In patients admitted to our intensive care unit, when the QTc interval is measured consecutively (daily), peak values are seen, on average, 2 to 3 days after admission. Because pathological QTc interval prolongation occurs in 2-3 days, the second ECG should be performed after 48 hours, and a patient with pathological prolongation must be followed closely.

There were a several limitations to the study. First, the sample size is relatively small. Although patients presenting with acute coronary syndrome were excluded from the study, myocarditis that might be associated with COVID-19 during their hospitalization and the effects of this condition on QTc were not clearly defined. Since the control group was not included in this retrospective study, the isolated contribution of COVID-19 infection to QTc prolongation could not be clearly determined.

Conclusion

In the patient population infected with COVID-19, the pathological QTc prolongation rate was 9.6%. In subgroup analyses, QTc interval lengthening was associated with high troponin levels and low GFRs. The risk of developing pathological QTc was significantly increased in patients with initial QTc ≥460 ms. Prolongation of QTc occurs on average at 2-3 days. Multiple factors cause QT prolongation in patients who are hospitalized and admitted to the intensive care unit. In addition to standard risk assessments, troponin levels and GFRs should be considered when evaluating patients with COVID-19.

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