CASE REPORT

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Adverse Cardiac Events Related to Hydroxychloroquine Prophylaxis and Treatment of COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19) was recognized as a pandemic by the World Health Organization (WHO) on March 11, 2020. The disease is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2/2019-nCoV). The measures to contain the spread of the disease such as social-distancing, hand hygiene, contact tracing, and isolation of persons suspected or confirmed to have the infection have been considered to be largely effective. No specific drugs for COVID-19 have been proven to be effective currently for either prophylaxis or treatment. However, hydroxychloroquine (HCQ) was suggested as one of the choices of the drug, despite the lack of evidence-based information. We present three case reports of cardiovascular adverse effects, with respect to its propensity to cause QT interval prolongation and potentially serious cardiac arrhythmias.

Keywords: hydroxychloroquine, cardiac, adverse, prophylaxis, treatment, covid-19.

INTRODUCTION

Hydroxychloroquine is commonly used for the treatment of rheumatic diseases because of its anti-inflammatory effects. It is a 4-amino-quinoline that is widely used for treatment purposes. The Scientific Advisory Board of Ministry of Health of Turkey for COVID-19 recommends HCQ for treatment and also for prophylactic use of COVID-19 (1). Infectious Diseases Society of America (IDSA) suggested the HCQ but also warned for the harmful effects (2). Turkish Society of Clinical Microbiology and Infectious Diseases cautioned against using HCQ for prophylaxis on March 21, 2020 (3). It is not recommended for prophylaxis in children under 15 years of age. It is contraindicated in individuals with retinopathy, known hypersensitivity, and pregnancy. This drug should be prescribed under close medical supervision, with monitoring for side effects, including QTc interval prolongation and cardiac arrhythmias (2).

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Identification of high-risk population and monitoring for prevention of such adverse events should be considered since it can lead to QT interval prolongation and *torsades de pointes* (TdP) in susceptible individuals. The risk of TdP is not a linear function of basal QTc or drug-induced prolongation in the QTc interval. FDA cautions against the use of HCQ for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. FDA is aware of reports of serious heart rhythm problems in patients with COVID-19 treated with HCQ, often in combination with azithromycin and other QT-prolonging medicines. This side effect is relatively rare, but co-prescription with other drugs such as azithromycin, which is also recommended for the treatment of COVID-19 could amplify the risk. Many other drugs such as quinolones, antihistamines etc. which are often used may also add to the risk of cardiac side effects. It interacts with other cardiac drugs such as beta-blockers and digoxin, which increases the blood levels of these drugs. It is recommended to have a baseline ECG to estimate the QTc interval in individuals receiving HCQ treatment (4). The normal upper limit for QTc interval is 460 ms for women and 450 ms for men (4).

Case 1

A 37-year-old female physician has been brought to the emergency department in the evening because of a sudden syncope attack with tachycardia and was transferred to Intensive care unit (ICU) with the diagnosis of supraventricular tachycardia and frequent ventricular extrasystoles. She has known to have hypertension and using nifedipine 30 mg once a day regularly. On the morning of her admission, she took one tablet of HCQ 200 mg for prophylaxis because of the contact with a COVID-19 positive patient. On the same day, she also received ciprofloxacin 500 mg po because of urinary tract infection. Her symptoms started around 12 hours after the HCQ intake. Her initial ECG at emergency room showed 180/min supraventricular tachycardia with frequent ventricular extrasystoles, QTc 120/min with elongation of 506 msn. Echocardiography showed normal left ventricular global systolic functions, valvular structures, with 70% ejection fraction, and with no pericardial effusion.

Diltiazem 25 mg 1x1 iv, diazepam 5 mg 1x1 iv were administered with the order of the cardiologist in an emergency. She was transferred to the ICU for monitorization. During her monitorization, the sinus rhythm was set after 12 hours and was started on metoprolol tartrate 25 mg po 2x1. She was discharged with a cardiac rhythm holter. During the 24-hour rhythm holter, the basic sinus was followed by a maximum heart rate of 120/min and a minimum heart rate of 62/min. During holter a total of 100 VES , 3 SVES, 3 trigemine beats were observed. Currently, she is still on metoprolol tartrate 25 mg of po 2x1 treatment.

Case 2

A 58-year-old male patient with COVID-19 PCR test positive result previously in another hospital was admitted to the emergency room with the complaint of tachycardia, muscle weakness and shortness of breath. He has a history of hypertension and using Ramipril and hydrochlorothiazide. At the time of admission, he was using HCQ 200 mg tb 2x1, azithromycin 500 mg once a day and oseltamivir 75 mg 2x1. His symptoms started 24 hours after the initial doses. His ECG revealed elongation of QTc with 500 msn and with PR range of 134 msn. He was admitted to the infectious diseases clinic, and medication was discontinued. The next day ECG showed QTc as 457 ms with PR interval of 134 ms. He was stabilized for his cardiac condition but needed to be hospitalized for 12 days for his infection and was discharged with recommendations.

Case 3

A 24-year-old physician without known any comorbidities was seen at an outpatient setting because of nausea, weakness and tachycardia. Her complaints had started after two doses of HCQ prophylaxis for COVID-19. Her heart rate was 110/min with sinus tachycardia, and QTc was 430 msn elongated. HCQ was discontinued and her complaints improved within a week.

DISCUSSION

Chloroquine phosphate and hydroxychloroquine sulphate are quinine derivative agents, which had been initially used for the treatment of malaria. After the discovery of the anti-inflammatory efficacy of these drugs, they have been used for the treatment of rheumatic diseases for their anti-inflam-

matory effects. It has been observed to inhibit ACE2 receptor-mediated entry of the virus by raising of intravesicular pH, affecting antigen processing, etc. along with inhibition of cytokine storm by its anti-inflammatory effects (5,6).

Retinal toxicity is the most well-recognized complication of long term use of these agents, but less frequently cardiac toxicity and neuro-myotoxicity could also occur. Risk factors for the development of HCQ-induced cardiac toxicity included older age, female sex, longer duration of therapy (>10 years), elevated per-kilogram daily dose, pre-existing cardiac disease, and renal insufficiency. In our cases, only one or two doses of HCQ were used (7).

The prophylaxis with HCQ in COVID-19 infection was suggested (8). However, in a recent study, the authors found no evidence that the use of hydroxychloroquine, either with or without azithromycin, reduced the risk of mechanical ventilation in patients hospitalized with Covid-19. They reported an association of increased overall mortality in patients treated with hydroxychloroquine alone (9).

In conclusion, at the 4th month of the pandemic, still, there is debate on how to use HCQ in both treatment and prophylaxis. If it is used, because of its potential risk of development of drug-associated cardiac arrhythmias, patients should be closely monitored. It is recommended to have a baseline ECG to define the QTc interval in individuals who are planned to receive HCQ treatment or prophylaxis for COVID-19.

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Conflict of Interest: The authors have no conflict of interest to declare.

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