CASE REPORT

Suspected Hydroxychloroquine-Induced Sinus Bradycardia and QTc Prolongation in a Patient with COVID-19

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Summary

An 84-year-old woman with hypertension, Alzheimer’s disease, and chronic kidney disease presented with fever and was diagnosed with corona virus disease 2019 (COVID-19). During the hospitalization, she experienced unexpected sinus bradycardia with prolonged QTc, which was thought to be closely related to the short-term use of hydroxychloroquine (HCQ), an old drug used to treat malaria and autoimmune diseases, but now used against COVID-19. The cardiac side effects of HCQ were rare, seen with short-term and low-dose use. With the COVID-19 pandemic, this case alerts clinicians to be aware of the arrhythmogenic effects of HCQ when it is used as an antiviral drug, especially in patients with preexisting cardiovascular diseases.

Key words: Coronavirus infections, Antiviral agents, Adverse effects

As the outbreak of the corona virus disease 2019 (COVID-19) progresses to a pandemic, effective prevention and treatment strategies are needed urgently at present and varieties of antiviral drugs are undergoing clinical trials against the fast-spreading virus.

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We report the case of an 84-year-old woman with hypertension, Alzheimer’s disease, and chronic kidney disease who was admitted because of COVID-19 infection, and experienced sinus bradycardia and QTc interval prolongation five days after hydroxychloroquine (HCQ) initiation. Such an abnormality disappeared days after HCQ withdrawal. This case alerts clinicians to be aware of the cardiac effects of antiviral drugs used to treat COVID-19.

Case Report

An 84-year-old woman who presented with fever for two days on February 4, 2020 was diagnosed with corona virus disease 2019 (COVID-19) using real-time fluorescence polymerase chain reaction (RT-PCR) tests of throat swab samples and chest computed tomography (Figure 1 A). She had hypertension for 10 years, Alzheimer’s disease for five years, and stage 4 chronic kidney disease (CKD) diagnosed two months ago. She showed no symptoms except mild dementia on admission. On a physical examination, her weight was 52 kg, the temperature was 37.3°C, the heart rate (HR) was 86 beats per minute (bpm), the blood pressure (BP) was 146/76 mmHg, the respiratory rate was 20 times per minute, and the oxygen saturation was 97%. Positive findings in laboratory tests included elevations in creatine of 360 μmol/L (normal range, 40-133 μmol/L), high-sensitivity cardiac troponin T (hs-cTnT) of 147.2 pg/mL (normal range, 0-14 pg/mL), and N-terminal pro B-type natriuretic peptide (NT-proBNP) of 5815 pg/mL (normal range 0-738 pg/mL). The electrocardiogram (ECG) monitoring revealed a sinus rate of 76 bpm, with right bundle branch block and left anterior fascicular block, and the QTc interval was 459 ms. Transthoracic echocardiography (TTE) revealed hypertrophy of the interventricular septum with a maximum thickness of 12 mm, but a normal cardiac chamber size and a left ventricular ejection fraction of 69%. Medical therapy included oral nifedipine (30 mg twice a day) and irbesartan (75 mg twice a day) for BP control, and darunavir and cobicistat tablets (800/150 mg once a day) as antiviral therapy. Continuous renal replacement therapy (CRRT) was initiated on the second day and performed daily because of the severe oliguria.

On the 15th day, during CRRT, she experienced asymptomatic hypotension (the lowest BP of 82/58 mmHg), which soon recovered after ceasing ultrafiltration and administering intravenous fluid supplementation. Hs-cTnT was elevated significantly to 699.5 pg/mL the next day.
and decreased gradually to a level less than 100 pg/mL in the following days, during which no changes were found on ECG and TTE. On the 25th day, the chest CT demonstrated an improvement in pneumonia, but there was a mild increase in pleural effusion (Figure 1B). However, no deterioration in her respiratory condition and no further elevation in NT-proBNP (3886 pg/mL) were found. As the RT-PCR tests for COVID-19 remained positive in samples of the throat swab and feces, we changed the darunavir and cobicistat tablets to hydroxychloroquine (HCQ) (200 mg twice a day). Over the next few days, her circulatory and respiratory conditions remained stable and no obvious changes in laboratory tests and ECG were revealed until the 30th day, on which her HR decreased unexpectedly to 51 bpm, and sinus bradycardia with prolonged QTc of 553 ms was revealed on ECG (Figure 2A). The potassium level was 4.2 mmol/L. The HCQ was discontinued and isoproterenol was given intravenously and titrated to a maximal dose of 10 mcg/minute. A fall in BP to less than 90/60 mmHg occurred hours later, and epinephrine was added at a maximal dose of 1 mcg/kg/minute, which maintained the systolic BP over 110 mmHg. In the following 24 hours, her HR still ranged between 40 and 50 bpm and ventricular fibrillation occurred. She was incubated and rescued by defibrillation. A temporary pacemaker was implanted to keep her HR higher than 60 bpm. The doses of isoproterenol and epinephrine were decreased gradually to withdrawal, and the pacing rate was set at 45 bpm in the following three days, during which her HR increased gradually over 60 bpm and QTc shortened. The QTc interval was normalized (450 ms) two days after isoproterenol and epinephrine withdrawal (Figure 2B), and was maintained over the following days of hospitalization.

**Discussion**

COVID-19 is a new disease that progresses rapidly to a pandemic. Evidence supported the fact that patients with preexisting cardiovascular diseases (CVDs) were more likely to be infected; vice versa, patients with COVID-19 were susceptible to myocardial damage. As for the present case, the causes of cTnT elevation might include CKD with low kidney clearance and chronic cardiac injury, COVID-19-associated inflammation and immune response, and hemodynamic disturbance mediated by CRRT. However, the mildly elevated cTnT was not associated with any changes on ECG, TTE, and symptoms.

HCQ and its predecessor chloroquine are old drugs used in the treatment of malaria and autoimmune diseases. Chloroquine could inhibit SARS-CoV83 and was tested for treating COVID-19 in clinical trials and recommended in the Chinese guidelines for COVID-19 management. The U.S. Food and Drug Administration granted emergency authorization for HCQ to treat COVID-19. However, it was reported to cause QT prolongation and decrease the resting HR. Although such proarrhythmic effects were rarely seen and occurred usually after chronic use, we could not definitely exclude such a link in our patient based on a few acute cardiac toxicity cases with low doses of HCQ use, and the association between the normalization of the heart rhythm and QTc and the HCQ withdrawal further demonstrated that. A literature review revealed a case of recent onset of complete atrioventricular block just two days after HCQ initiation to treat systemic lupus erythematosus. Additionally, an acute cardiac arrest nine hours after HCQ initiation for malaria was reported in a patient with hypertension treated with amiodipine. The possible explanations raised by the authors included the adverse effects of vasodilation and hypotension of both drugs, and the complex drug interaction.

Although some experts recommended a dose reduction for patients undergoing hemodialysis, others suggested that no dosage adjustment was necessary for short-term use for COVID-19 treatment. A lower dosage is reasonable for patients with impaired renal function as HCQ is substantially excreted by the kidneys and because of the risk of toxic reactions with other drugs. Further studies are needed to delineate the optimal effective and safe dose for COVID-19 treatment, especially in patients who are elderly, and have CKD and preexisting CVDs.

**Conclusions**

Myocardial protection should be one of the major concerns during treatment strategy planning for COVID-
Furthermore, clinicians should carefully assess the risks and benefits to avoid adverse cardiac effects before prescribing antiviral drugs, especially in patients with pre-existing CVDs and myocardial injury.

**Disclosure**

**Conflicts of interest:** The authors have no conflict of interest to disclose.

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