Hydroxychloroquine-Induced QT Prolongation in a COVID-19–Positive Patient on Clozapine

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Hydroxychloroquine, an antimalarial medication, was approved in March 2020 by the US Food and Drug Administration (FDA) for treatment of hospitalized patients with coronavirus disease 2019 (COVID-19) infection.[1] This drug is used in the treatment and prevention of malaria, a mosquito-borne disease caused by a parasite. It is also used to treat discoid lupus erythematosus, systemic lupus erythematosus, and rheumatoid arthritis due to its capacity to decrease the activity of the immune system.[2] Despite widespread clinical use of hydroxychloroquine, insights into the mechanism of action of these drugs are still emerging. This drug interferes with lysosomal activity and autophagy, interacts with membrane stability, and alters signaling pathways and transcriptional activity, which can result in inhibition of cytokine production and modulation of certain costimulatory molecules. As all other medications, hydroxychloroquine can also cause some side effects. Side effects, also known as adverse events, are unwanted or unexpected events or reactions to a drug. Some of the side effects associated with the use of this medication include hemolysis, retinopathy, bone marrow failure, agranulocytosis, and QT prolongation.[3]

The QT interval is the time from the start of the Q wave to the end of the T wave. It represents the time taken for ventricular depolarization and repolarization. It is inversely proportional to heart rate. QT is prolonged if > 450 ms in men or > 460 ms in women.[4] A number of causes including electrolyte imbalance as well as medications/drugs can lead to QT prolongation. Antipsychotic medications have long been known to have the potential to cause QT prolongation and torsades de pointes. Retrospective and cohort studies[5] have linked antipsychotic use with sudden cardiac death, and most antipsychotic medications have been shown to cause some degree of QT prolongation.

Table 1. Risk Factors for Prolonged QT[a]

Female sex
Increased age
Congenital LQTS
Electrolyte abnormalities
Hypokalemia
Hypocalcemia
Hypomagnesemia
Anorexia nervosa*
Diuretic use*
Heart conditions
Bradycardia
Left ventricular dysfunction
Heart failure
Mitral valve prolapse
Myocardial infarction
Other medical conditions
Renal dysfunction*
Hepatic dysfunction
Hypoglycemia*
Hypertension**
Diabetes*
Hypothyroidism*
Pituitary insufficiency*
CNS injury (stroke, trauma, tumor, infection)*
AIDS
Malnutrition*
Obesity (including acute weight gain)*

[a]Reprinted with permission from Beach et al.[10]
*Causes QTc prolongation via effects on electrolytes.
**Causes QTc prolongation via diastolic dysfunction.
Abbreviations: CNS = central nervous system, LQTS = long QT syndrome.

Case Report

The patient was a 45-year-old, single, unemployed Hispanic woman who was currently on assisted outpatient treatment. She had a psychiatric history of schizoaffective disorder and a past medical history significant for hypertension, diabetes mellitus, and hyperlipidemia. She was transported from her residence to the comprehensive psychiatric emergency program (CPEP) by the fire department due to suicidal thoughts. At the time of initial evaluation, she was very guarded and labile. She was slow, with blocked thought process, and was internally preoccupied, reporting auditory hallucinations telling her that the medications were not good. She also reported poor appetite and sleep.

She was unable to give relevant information regarding signs and symptoms of COVID-19; nevertheless, she was placed in isolation while in CPEP due to a fever of 101°F. She was also restarted on her home medications, which included mirtazapine, lithium, risperidone, metoprolol, metformin, atorvastatin, docusate, and clozapine. An electrocardiogram (EKG) was done at admission and showed a corrected QT (QTc) of 393 ms, and a PCR (polymerase chain reaction) test was positive for COVID-19. The patient was then transferred to the inpatient psychiatry COVID unit. There, she was seen by the medical team, and they recommended

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Table 2. Nonpsychiatric Medications Associated With QTc Prolongation[a]

Antiarrhythmics
Class I
Quinidine
Disopyramide
Procainamide
Class III
Sotalol
Amiodarone
Dofetilide
Antibiotics
Macrolides
Erythromycin
Clarithromycin
Azithromycin
Quinolones
Levofloxacin
Moxifloxacin
Antifungals
Fluconazole
Ketoconazole
Other antibiotics
Pentamidine
Antimalarials
Chloroquine
Halofantrine
Other medications
Tamoxifen
Vandetanib
Furosemide
Terfenadine (withdrawn due to TdP)
Cisapride (withdrawn due to TdP)
Methadone

[a]Reprinted with permission from Beach et al.[10]
Abbreviation: TdP = torsades de pointes.

Table 3. QTc Prolongation Risk Stratification for Commonly Used Antipsychotic Medications[a,b]

	Association With QTc Prolongation	Association With Torsades de Pointes
High risk		
Thioridazine	+++	+++
Haloperidol (IV)	+++	+++
Ziprasidone	+++	+
Moderate risk		
Fluphenazine	++	—
Haloperidol (PO/IM)	++	++
Iloperidone	++	—
Paliperidone	++	—
Risperidone	+	+
Low risk		
Asenapine	+	—
Lurasidone	+	—
Olanzapine	+	+
Quetiapine	+	+
Minimal risk		
Aripiprazole	—	—

[a]Reprinted with permission from Beach et al.[10]
[b]The relative risks for QTc prolongation may vary depending on dose, concomitant medications, and other medical illnesses.
Abbreviations: IM = intramuscularly, IV = intravenous, PO = orally.

hydroxychloroquine 400 mg plus azithromycin 500 mg by mouth daily for 3 days, droplet and contact isolation, and chest x-ray, as well as to stop risperidone and clozapine and monitor her QTc interval. On days 2 and 3 after starting treatment with hydroxychloroquine, her QTc was 481 ms and 486 ms, respectively. On days 2 and 7 posttreatment, her QTc was 479 ms and 451 ms, respectively. Then, clozapine was restarted and slowly titrated up. The patient's psychiatric condition improved considerably after a week, and she was able to be discharged safely to the community.

Discussion

This case shows an increase in QTc interval caused by hydroxychloroquine, which was also reported by Saleh et al.[6] The increase in QTc could have been worse in our patient if clozapine was not stopped during this time.

A systematic review and meta-analysis published by Ullah et al[7] regarding hydroxychloroquine for the treatment of COVID-19 showed no benefits, while Meo et al[8] suggested that hydroxychloroquine can successfully treat COVID-19 infections. Despite the controversy, this case aims to shed light on the importance of monitoring QTc via EKG in patients receiving hydroxychloroquine.[9] More importantly antipsychotics should be avoided while patients are receiving this medication, since both hydroxychloroquine and most antipsychotics can increase the QTc. Holding clozapine and risperidone while our patient was being treated for COVID-19 decreased the potential negative impact on the QTc. Beach et al[10] described the risk factors for prolonged QT, the nonpsychiatric medications associated with QTc prolongation, and the QTc prolongation risk stratification for commonly used antipsychotic medications (Tables 1–3). The half-lives of the medications in question must be taken into consideration. The elimination half-life of clozapine averages approximately 14 hours under steady-state conditions, but there is substantial variability across individuals.[11] In poor metabolizers, the half-life of risperidone is about 19 hours compared with about 3 hours in extensive metabolizers.[12] Hydroxychloroquine has a prolonged half-life, between 40 and 50 days.[13]

Conclusion

The COVID-19 pandemic has caused more than 700,000 deaths around the globe and more than 150,000 deaths in the United States. Psychiatric patients are also being hospitalized and receiving treatment with hydroxychloroquine. Holding antipsychotics and monitoring the QTc interval via EKG results are crucial to limit the adverse effect of QT prolongation of both medications.

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