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Effects of cardiac toxicity of combination therapy with hydroxychloroquine and azithromycin in COVID-19 patients

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ABSTRACT

Coronavirus disease 2019 (COVID-19), which began in China, caused a global pandemic. Few studies have shown the benefit of hydroxychloroquine (HY) ± azithromycin (AZ) for treating COVID-19. Concerns of QT prolongation and increased risks of torsade's de pointes (TdP) with this combination have been raised since each agent can individually prolong the QT interval. This retrospective, observational study included hospitalized patients treated with HY and AZ from March 2020 to May 2020 at a large community hospital. Serial assessments of the QT interval were performed. Our aim is to evaluate the safety and characterize the change in QTc interval and arrhythmic events in COVID-19 patients treated with HY/AZ. A total of 21 COVID patients who received at least four days of HY and AZ were included in this study. Mean baseline was QTc 403 ms, mean maximum QTc was 440 ms, mean change in QTc was 36 ms. Only one patient (4.8%) developed prolonged QTc > 500 ms. No patient had a change in QTc of 60 ms or more. No patient developed TdP. Fifteen patients (71.4%) had hypoxia on admission, with only two patients (9.5%) required oxygen of 1–2 L at discharge. 80.9% of patients have been discharged home or inpatient rehabilitation.

Introduction

Coronavirus disease 2019 (COVID-19) has caused global anxiety and resulted in several deaths [1]. Multiple antivirals have been proposed to decrease mortality related to COVID-19. Drugs like hydroxychloroquine (HY) and azithromycin (AZ) have been tested for their potential against coronavirus [2–5]. Several studies addressing the efficacy and safety of HY and AZ were conducted in COVID-19 patients leading to contradictory results. QT prolongation [6] and torsade's de pointes (TdP) with these medications were concerning. Therefore, we aimed to examine the safety of HY with AZ in patients with COVID-19.

Methods

This evaluation is an Institutional Review Board (IRB) exempt retrospective, observational study performed in an 1100 bed large community hospital. Data were retrieved and deidentified from electronic medical records. Our study included 21 patients. All COVID-19 patients from March 2020 to May 2020 who received at least 250 mg of daily azithromycin and a loading dose of 400 mg of HY on the first day followed by 200 mg once daily were included. Patients received at least 4 days of HY and AZ. Among 21 patients, 18 patients received a total of 5 days of HY/AZ during hospitalization, 3 patients (14.3%) were discharged home before completing 5 days course as they recovered well and were instructed to take the remaining one more dose of HY/AZ at home. Patients included in this review are >18 years of age, confirmed COVID-19 by positive reverse transcription-polymerase chain reaction (RT-PCR), and had adequate follow-up information for evaluation. We have excluded patients with prolonged QTc > 500 ms. An infectious disease-specialized pharmacist and physician-reviewed medication administrations and treatment responses. Electrocardiograms were manually evaluated to calculate QTc intervals using the Bazett formula. The QTc interval was continuously monitored with a daily recorded electrocardiogram and continuous telemetry. Collected data include demographic information, QTc change, peak QTc, laboratory values, symptoms, length of stay, oxygen requirement at admission, and discharge. The primary outcome was TdP. Sec-

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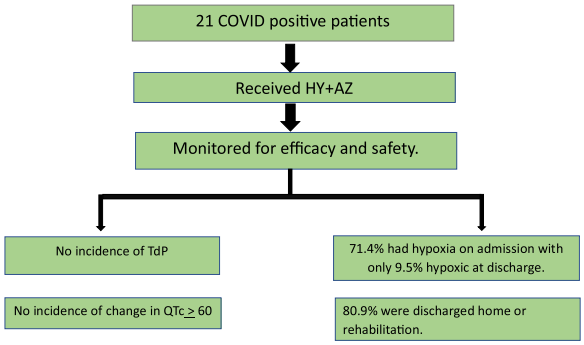

Fig. 1. Primary and secondary outcomes.

ondary outcomes included survival with weaning from oxygen and discharge from hospital to home or inpatient rehabilitation (Fig. 1).

Results

A total of 21 patients met the inclusion criteria for evaluation. Mean age was 58.7 (range 23–88), 12 were males (57.1%), 10 were Caucasians (47.6%), 8 were African Americans (38.1%), 3 were Hispanics (14.3 %), mean weight was 95.2 kgs (range 17.8–50.6), mean BMI was 32.8 (range 17.8–50.6). The overall mean baseline was QTc 403 (range 369–458) ms, mean maximum QTc was 440 (range 406–504) ms, mean change in QTc was 36 (19–49) ms, mean HR was 81 (range 71–95). Only one pt (4.8%) developed prolonged QTc > 500 ms. No patient had a change in QTc of 60 ms or more (Table 1).

Baseline ECG of 20 patients (95.2%) was sinus rhythm. Only one patient (4.8%) had left bundle branch block (LBBB). On arrival 20 patients (95.2%) had shortness of breath, 21 patients (100%) had cough, 18 patients (85.7%) patients had fever, 3 patients (14.3%) had chest pain, 8 patients (38%) had diarrhea, 6 patients (28.6%) had decreased appetite, 8 patients (38%) had nausea, 4 patients (19%) had vomiting. 12 patients (57.1%) had hypertension, 2 patients (9.5%) had diabetes, 2 patients (9.5%) had coronary artery disease, 2 patients (9.5%) had congestive heart failure, no patients had atrial fibrillation. Mean admission white blood cell (WBC) was 8×10^3/mcL, mean maximum WBC was 12×10^3/mcL, mean discharge WBC was 8.6×10^3/mcL.

100% patients had pneumonia, 10 patients (47.6%) were admitted to intensive care unit (ICU), 2 patients (9.5%) required vasopressor, 6 patients (28.6%) required ventilator, only 1 patient (4.8%) developed acute respiratory distress syndrome (ARDS) and 1 patient (4.8%) developed pulmonary embolism. 15 patients (71.4%) had hypoxia on admission, with only 2 patients (9.5%) requiring 1-2 L oxygen at discharge. 3 patients above 80 years of age with multiple comorbidities were made comfort care. 17 patients (80.9%) were discharged home or inpatient rehabilitation. Overall mean length of stay is 10.8 days (range 4–31).

The primary outcome of TdP was not observed in the entire population. 80.9% of patients have been discharged home or inpatient rehabilitation, with only 9.5% requiring 1–2 L oxygen at discharge which is the secondary outcome.

Discussion

Several pharmacologic intervention strategies have been proposed for the management of COVID-19 in hopes of decreasing morbidity and mortality. One such therapy currently under study in humans is the use of HY/AZ [7]. A significant concern with the use of this therapy has been the risk of QT prolongation and TdP. In a study conducted in New York [8] on 201 COVID-19 patients treated with chloroquine/hydroxychloroquine and azithromycin, QT prolongation was found to be a side effect of these drugs, but clinicians rarely had to stop treatment, and TdP or arrhythmogenic mortality was not observed. A meta-analysis study [9] also found a slight but not statistically significant increase in arrhythmias and QT prolongation when HY and AZ were administered combined versus HY alone. In our study, we gave HY/AZ to patients whose baseline QTc was <500 ms. No patient had a change in QTc of 60 ms or more. No patient developed TdP. Only one patient (4.8%) developed prolonged QTc > 500 ms. This patient is a 78 yo male with a known history of alcohol abuse and systolic heart failure with EF 25–30%, whose baseline EKG showed LBBB with a baseline QTc interval of 458 ms. Loop diuretics, which were independently associated with prolonged QTc, were given to this patient as he was volume overloaded with an elevation of QTc to 504 ms on the second day, with a drop of QTc to 459 ms on the 6th day.

Yao et al. [10] study shown that chloroquine and hydroxychloroquine inhibit severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro, with hydroxychloroquine being more potent than chloroquine. Report from France [11] documented viral load reduction or disappearance in COVID-19 patients treated with HY and AZ. These results were interesting, so in our study, we focused on clinical outcomes in COVID-19 patients treated with HY, AZ, in addition to close monitoring of QTc. Our study results showed that 15 patients (71.4%) had hypoxia on admission, with only two patients (9.5%) requiring 1–2 L oxygen at discharge. 80.9% of patients have been discharged home or inpatient rehabilitation.

Table 1
Characteristics of the patients.

Variable	Total (N = 21)
Demographic characteristics	
Age, mean, (range), yr	58.7 (23–88)
Male, no. (%)	12 (57.1%)
Hispanics, no. (%)	3 (14.3%)
Caucasian, no. (%)	10 (47.6%)
African American, no. (%)	8 (38.1%)
Weight, mean (range) kg	95.2 (17.8–50.6)
BMI, mean (range)	32.8 (17.8–50.6)
Comorbidities	
Hypertension, no. (%)	12 (57.1%)
Diabetes, no. (%)	2 (9.5%)
CHF, no. (%)	2 (9.5%)
CAD, no. (%)	2 (9.5%)
Atrial fibrillation, No.	0
Symptoms	
Shortness of breath, no. (%)	20 (95.2%)
Cough, no. (%)	21 (100%)
Fever, no. (%)	18 (85.7%)
Diarrhea, no. (%)	8 (38%)
Chest pain, no. (%)	3 (14.3%)
Decreased appetite, no. (%)	6 (28.6%)
Nausea, no. (%)	8 (38%)
Vomiting, No. (%)	4 (19%)
Electrocardiograms	
Sinus rhythm, no. (%)	20 (95.2%)
Baseline heart rate, mean(range)	81 (71–95)
Baseline QTc, mean (range) ms	403 (369–458)
ΔQTc, mean (range), ms	36 (19–49)
Peak QTc>500, no. (%)	1 (4.8 %)
Maximum QTc, mean (range), ms	440 (406–504)
TdP, no.	0
Organ support	
Invasive mechanical ventilation, No. (%)	6 (28.6%)
Vasoactive drugs, no. (%)	2 (9.5%)
Admission WBC count, mean /mcL	8 × 103
Maximum WBC count, mean /mcL	12 × 103
Discharge WBC count, mean /mcL	8.6 × 103
Hypoxia on admission, no. (%)	15 (71.4%)
Hypoxia at discharge, no. (%)	2 (9.5%)
Length of stay, mean (range) d	10.8 (4–31)

Key limitation of our study is that it is a small retrospective observational study. Potential confounding variables, such as drugs that can prolong or shorten the QTc interval, were not assessed. Additional work is needed to confirm our findings in an even larger group of patients.

Risks of QT prolongation may be higher in critically ill, hospitalized COVID-19 patients with metabolic derangements and other medications, increasing the risk of drug-drug interactions [12,13]. Further studies are needed to confirm the possible protective benefits and safety profile of HY/AZ for the treatment of COVID-19 patients. Clinical trials are ongoing, and new information will likely be added to the existing literature soon, necessitating updating this review.

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Competing interests

None declared.

Ethical approval

Not required.

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