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ORIGINAL ARTICLE

# Medication safety in a pandemic: A multicentre point prevalence study of QTc monitoring of hydroxychloroquine for COVID-19

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## Abstract

**What is known and Objective:** A pandemic can strain all aspects of the healthcare system, including the ability to monitor the safety of medication use. Reviewing the adequacy of medication safety practices during the COVID-19 pandemic is critical to informing responses to future pandemics. The purpose of this study was to evaluate medication safety practices at a height of both COVID-19 cases and hydroxychloroquine use.

**Methods:** This was a multicentre observational point prevalence study. Adult inpatients receiving hydroxychloroquine for COVID-19 between March 22 and 28, 2020 were included. The primary outcome was the percentage of patients receiving appropriate QTc monitoring. Secondary outcomes included QTc prolongation, early discontinuation of hydroxychloroquine and ventricular arrhythmias.

**Results and discussion:** A total of 59% (167/284) of patients treated with hydroxychloroquine received appropriate QTc monitoring. QTc prolongation occurred in 25%. Hydroxychloroquine was prematurely discontinued in 1.4% of patients, all due to QTc prolongation. Ventricular arrhythmia occurred in 1.1%.

**What is new and Conclusion:** Medication safety practices were suboptimal with regard to hydroxychloroquine monitoring at the height of the COVID-19 pandemic. Preparation for future pandemics should devote considerable attention to medication safety.

KEYWORDS
Covid-19, drug monitoring, hydroxychloroquine, medication safety, pandemic

## 1 | WHAT IS KNOWN AND OBJECTIVE

The COVID-19 pandemic has put extraordinary pressure on all aspects of the healthcare system around the world. As of February 6, 2021, there have been over 100 million confirmed infections and over 2 million deaths.[1] The considerable morbidity and mortality among those with severe disease has driven a critical need for effective therapies. Particularly in the beginning of the pandemic, this

  

created an environment ripe for widespread use of unproven medications. One of the earliest of these was the use of hydroxychloroquine with or without azithromycin.

Initially, evidence supporting chloroquine-based management of COVID-19 infection was drawn from in vitro studies.[2] The first clinical study by Gautret et al. popularized not only hydroxychloroquine but also combination therapy with azithromycin.[3] Although the studies published were methodologically flawed,[4] these findings had amonumental impact on COVID-19 treatment worldwide. These publications, in addition to the U.S. presidential press conference highlighting their results, were followed by dramatic increases in internet searches[5] and prescription fills[6] for hydroxychloroquine. Subsequent, higher quality studies have consistently found no benefit with the use of hydroxychloroquine with or without azithromycin for the treatment of COVID-19 infection.[7-9]

An advantage of repurposing medications during a pandemic is the potentially well-known safety profiles of these therapies. Hydroxychloroquine and azithromycin are generally well tolerated; however, both drugs inhibit the delayed rectifier potassium current, delaying cardiac repolarization.[10] Both drugs have been linked to QTc prolongation which is associated with Torsades de pointes (TdP), other ventricular arrhythmias and sudden cardiac death.[11] Several patient-specific factors can increase the risk for QTc prolongation including age, gender, comorbidities and electrolyte abnormalities. Both hydroxychloroquine and azithromycin are considered nonantiarrhythmic drugs with known risk for TdP.[12] When initiating these drugs in patients with underlying risk factors for TdP, the American Heart Association recommends baseline and subsequent electrocardiogram (ECG) monitoring to minimize the risk of QTc prolongation and arrhythmia.[11]

Appraising practices from this pandemic are key to identifying opportunities to improve responses to future pandemics. With overwhelming numbers of cases and strained resources, providers may not have approached medication safety with the same diligence as they would have outside of a pandemic. The purpose of this study was to evaluate medication safety practices at a height of both COVID-19 cases and hydroxychloroquine use.

## 2 | METHODS

This was a retrospective point prevalence study conducted at 4 hospitals within a New Jersey health system. These hospitals range in bed size from 332 to 597, and include both teaching and non-teaching community hospitals. Inpatients who tested positive for SARS-CoV-2 by nasopharyngeal PCR between 22 March 2020 and 28 March 2020 and were treated with hydroxychloroquine for greater than 2 days were included in the study. Patients receiving hydroxychloroquine for an alternative indication or not requiring QTc monitoring (due to a lack of risk factors for QTc prolongation) were excluded. The presence of risk factors included in the Tisdale Risk Score was used to determine the requirement for QTc monitoring. This particular date range was chosen due to a peak of both COVID-19 cases in the area and attention on hydroxychloroquine from both the scientific and public communities.[5]

During this time period, health system guidance at the study hospitals on treatment of COVID-19 recommended hydroxychloroquine 400 mg every 12 h × 2 doses on day 1, followed by 400 mg once daily on days 2–5 for all patients who did not have contraindications. QTc monitoring was recommended but no particular guidance on monitoring frequency was provided. Decisions regarding treatment and monitoring were subject to the discretion of the care team.

The primary outcome of this study was to determine the percentage of patients who received appropriate QTc monitoring among those in which it was indicated. Appropriate monitoring was defined as a baseline ECG prior to treatment and either a follow-up ECG within 48 h of treatment initiation or continuous cardiac monitoring during therapy.[11] Tisdale risk scores, which predict the risk of QTc prolongation, were calculated for each patient.[12] The Tisdale Risk Score calculation was modified to expand the list of drugs considered to be QTc-prolonging, consistent with CredibleMeds. This included the addition of hydroxychloroquine and azithromycin among other medications.[13] Secondary outcomes included QTc prolongation (defined as any QTc ≥500 ms or a ≥60 ms increase in QTc), discontinuation of hydroxychloroquine due to an adverse drug event, and ventricular arrhythmias. Causality was assessed using the modified World Health Organization (WHO)—Uppsala Monitoring Centre (UMC) Causality Categories.[14] Severity of illness was assessed as the highest severity over the course of the admission. Descriptive statistics were used to analyse the outcomes. The local institutional review boards approved the study.

## 3 | RESULTS AND DISCUSSION

A total of 353 patients tested positive for SARS-CoV-2 and were hospitalized for greater than 48 h during the study period. Hydroxychloroquine was administered to 284 (80%) patients for greater than 48 h. QTc monitoring was indicated in 283 (99.6%). The most common risk factors for QTc prolongation were concomitant use of QTc prolonging medications (278/283, 98.2%), age greater than 67 years (113/283, 39.9%), loop diuretic use (109/283, 38.5%), baseline QTc ≥450 ms (93/283, 32.9%), hypokalaemia (87/283, 30.7%) and sepsis (66/283, 23.3%). The most common concomitant QTc-prolonging medications were azithromycin (271/283, 95.8%), propofol (70/283, 24.7%) and ondansetron (41/283, 14.5%). The mean patient age was 63.1 years (SD 15.8) and 115 (40.6%) patients were female. Diabetes (105/283, 37%) was the most common comorbidity. Severity of illness was 6.4% (18), 34.3% (97) and 59.4% (168) mild/moderate, severe and critical, respectively. One hundred fifteen (40.6%) patients required ICU admission during hospitalization. The mortality rate was 40.6% (115/283).

A total of 167(59%) of those treated with hydroxychloroquine received appropriate baseline and follow-up QTc monitoring. Fifty-three (18.7%) did not have a baseline ECG obtained and 77 (27.2%) did not have a follow-up ECG within 48 h or continuous cardiac monitoring.

Among those with baseline and follow-up ECG monitoring, QTc prolongation occurred in 25% (23/92). This included 22% (20/92) with QTc ≥500 ms and 14% (13/92) with a QTc change ≥60 ms. QTc prolongation occurred in 0% (0/10), 23.9% (14/59) and 39.1% (9/23) of patients with low, medium and high Tisdale risk scores. Hydroxychloroquine was prematurely discontinued in 1.4% (4/283) of patients, all due to QTc prolongation. Ventricular arrhythmia occurred in 3 patients (1.1%). The first 2 cases, consisting of premature ventricular complexes and non-sustained ventricular tachycardia, respectively, resolved without treatment. One case of ventricular tachycardia resulted in cardiac arrest with a fatal outcome. All cases were assessed as possibly related to hydroxychloroquine according to the WHO-UMC Causality Categories.

## 4 | DISCUSSION

In this study, there was widespread use of medications ultimately proven to be ineffective for the treatment of COVID-19 infection. Eighty percent of patients hospitalized for ≥48 h during the study period received hydroxychloroquine and 95.8% of those received combination therapy with azithromycin. QTc monitoring was indicated in 99.6%, nearly all patients who received hydroxychloroquine. While the evidence regarding the efficacy of hydroxychloroquine and azithromycin for COVID-19 was inconclusive at the time, the safety profiles and monitoring requirements of each drug were well known. Despite this, there were suboptimal medication safety practices at the peak of the pandemic.

Other studies have reported on medication safety practices during the pandemic and found variable results. In a cohort study conducted at an academic tertiary care centre by Mercuro et al, 71 out of 90 (79%) patients started on hydroxychloroquine with or without azithromycin for COVID-19 had follow-up ECG performed after starting therapy.[15] A case series performed in a tertiary academic medical centre by Ramireddy et al found that inpatients administered azithromycin and/or hydroxychloroquine had a baseline ECG available in only 192 out of 314 patients (61%). Further, only 98 out of 192 patients (51%) had follow-up ECGs performed despite hospital policy requiring daily ECGs in all patients started on hydroxychloroquine.[16] In contrast, Saleh et al reported 100% compliance with baseline and follow-up ECG monitoring in 201 patients treated at 3 hospitals in a New York health system.[17] As is the case with our study, all of these studies were conducted during the height of the pandemic when institutions would seemingly be most vulnerable to suboptimal medication safety practices. Yet, low rates of appropriate ECG monitoring have also been identified outside of a pandemic setting. Both Daniel et al[18] and Hutchins et al[19] reported low baseline compliance with QTc monitoring for inpatients receiving QTc-prolonging drugs at 42% and 47.8%, respectively. Clearly, inadequate QTc monitoring is not a problem unique to this pandemic.

Nonetheless, the pandemic setting brings unique challenges to medication safety, including limited human resources to conduct testing and limited supply of personal protective equipment (PPE). Therefore, creative monitoring strategies may be particularly useful. Giudicessi et al proposed smartphone-enabled mobile ECG monitoring to limit personnel exposure and conserve PPE.[20] The aforementioned study conducted by Saleh et al, which had uniform compliance with QTc monitoring, described the use of mobile cardiac outpatient telemetry patches to monitor QTc in patients on non-telemetry units.[17] More than half of their cohort was monitored via this method. This high compliance likely reflects a rigorous health system-wide monitoring plan that was flexible enough to maintain feasibility during the pandemic surge. Such planning is key to maintaining high quality medication monitoring during a pandemic.

QTc prolongation was fairly common in this cohort, occurring in 25% of patients with adequate monitoring. Other studies have found rates ranging from 5 to 33%.[15-17,21-23] Notably, QTc intervals in our study were automatically calculated and not manually adjudicated which may impact the accuracy of these results. Adverse outcomes were rare which is consistent with previous studies. Yet, adverse event identification may have been hindered by suboptimal monitoring or incomplete clinician documentation during the pandemic. Therefore, these safety outcome rates should be interpreted with caution.

## 5 | WHAT IS NEW AND CONCLUSION

Reflecting on the COVID-19 pandemic is critical to identifying enduring lessons for future pandemics. It is impossible to know what repurposed drugs will show promise as treatments for the next pandemic. Yet, their toxicities may be well known. Seymour et al call for clinicians to practice sensible medicine amidst the COVID-19 pandemic.[24] They offer several strategies, including elevating usual care and focusing on practices with known patient benefits. In this study, there was widespread use of unproven medications and inadequate medication monitoring at the height of the COVID-19 pandemic. Adverse outcomes were rare, although this is difficult to know with certainty due to limitations in monitoring. Preparation for the next pandemic must include an emphasis on practices known to improve patient outcomes, including a significant attention to medication safety.

## 6 | PATIENT CONSENT

Not applicable.

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### CONFLICTS OF INTEREST

The authors have no relevant conflicts of interest to disclose.

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