Original Article

Seven day continuous ambulatory electrocardiographic telemetric study with pocket electrocardiographic recording device for detecting hydroxychloroquine induced arrhythmias

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Abstract

Objective: The use of hydroxychloroquine (HCQ) for COVID-19 treatment and prophylaxis raised issues concerning its cardiac safety owing to the possibility of QT prolongation and arrhythmias. There was no study on long-term electrocardiographic telemetry monitoring of patients taking HCQ. We planned a continuous electrocardiographic Holter telemetry of these patients for 7 days. **Material and Methods:** Health care workers taking HCQ as pre exposure prophylaxis and patients on HCQ were monitored using seven day Holter electrocardiographic telemetry with continuous beat to beat analysis. Telemetry can instantly convey any arrhythmic event or significant QT prolongation to the medical faculty. **Results:** Twenty-five participants with a mean age of 42.4 ± 14.1 years were included in the study; 40% were females. Twenty percent of participants needed to stop HCQ. Four patients developed QT prolongation >500 ms and needed to stop HCQ, one patient had accelerated idioventricular rhythm and stopped treatment, and one had short episodes of atrial fibrillation. No malignant arrhythmia or ventricular arrhythmia, or torsade de pointis were noted. No episode of significant conduction disturbance and arrhythmic death was noted. Baseline mean QTc was 423.96 ± 32.18 ms, mean QTc corrected at 24 h was 438.93 ± 37.95, mean QTc was 451.879 ± 37.99 at 48 h, and change in baseline mean QTc to max QTc was 30.74 ± 21.75 ms at 48 h. All those who developed QTc prolongation >500 ms were greater than 50 years of age. **Conclusion:** Ambulatory telemetry ECG monitoring detects early QT prolongation, and stopping drugs prevents malignant arrhythmias. HCQ seems to have less risk of QT prolongation in young, healthy individuals.

Keywords: COVID-19, hydroxychloroquine, QT prolongation, telemetry

Introduction

The use of hydroxychloroquine (HCQ) for COVID-19 treatment and prophylaxis raised issues concerning its cardiac safety owing to the possibility of QT prolongation and arrhythmias.[1,2] HCQ has been used to treat malaria, lupus, and rheumatoid arthritis. Quinidine, a group member involving HCQ, is one of most torsades de points (TDP) causing drugs.[3] Some reports of the arrhythmic potential of HCQ have been reported. However, the exact frequency of events is underreported,[3] and the exact incidence of drug-induced TDP with HCQ is unknown. Inhibition of iKr and resultant QT prolongation associated with

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HCQ can induce TDP and cause sudden cardiac death.[3,4] There is a lack of reliable data on this subject, and the risk of widespread unsupervised use in the present-day COVID pandemic is high. The half-life of HCQ is around 40 days.[5] There has been no study on long-term electrocardiographic monitoring of patients taking HCQ. We planned continuous electrocardiographic telemetry of these patients for 7 days.

Aims and Objectives

1. To assess QT prolongation to dangerous levels in patients on HCQ
2. To detect cardiac arrhythmias early and take preventive measures to prevent sudden cardiac death

Methods

We conducted a prospective observational cohort study at a tertiary care hospital. Healthy healthcare workers taking pre-exposure COVID-19 HCQ prophylaxis and patients taking HCQ for treatment with written informed consent were included. The decision to take HCQ as prophylaxis and treatment was based on hospital COVID policy and patient preference. People with a corrected QT of >480 ms, known congenital long QT, people who were having comorbidities and contraindications to HCQ such as retinopathy, known hypersensitivity to chloroquine, cardiomyopathy, prolonged QTc, cardiac arrhythmias, history of psoriasis, porphyria cutanea tarda, epilepsy, myasthenia gravis, myopathy of any cause, serious hepatic or renal disease, known glucose-6-phosphate dehydrogenase deficiency, current use of medication with known serious hepatotoxic effects or known interaction with chloroquine, severe depression, electrolyte imbalance, antiarrhythmic drugs, and those with cardiac devices such as pacemakers and defibrillators were excluded. The Indian Council of Medical Research, under the Ministry of Health and Family Welfare, has recommended chemoprophylaxis with HCQ (400 mg twice on day 1, 400 mg once a week thereafter) for asymptomatic healthcare workers treating patients with suspected or confirmed COVID-19 and for asymptomatic household contacts of confirmed cases. For treatment, HCQ 400 twice a day for the first day followed by 400 mg once a day for ten days was used.[6]

Pocket ECG (Medicalalgorithmics) constantly captures and classifies every heartbeat, records the onset and offset of every arrhythmia, and detects all ventricular and supraventricular arrhythmias. The report is transmitted via a satellite network to physicians and allows continuous remote monitoring. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki (2001). The study protocol was approved by the ethics committee on human research of the institute and registered with the clinical trials registry of India (CTRI/2020/05/025216, 16/05/2020). All patients provided written informed consent before inclusion in the study.

Variables

Primary endpoints were to analyze the incidence of QT prolongation by 25% of baseline and the number of patients with QT prolongation >500 ms and ventricular arrhythmias. Secondary endpoints were to study drug-related adverse effects. Continuous electrocardiographic telemetry electrocardiography was used, and physicians were alerted immediately when dangerous levels of QT prolongation or arrhythmia events were noted.

Statistical methods

Continuous variables were reported as mean ± SD, and categorical variables were reported as numerical values and percentages. Paired t test was used to compare the difference in QT c from baseline to maximum values.

Results

Participants

Out of 200 healthcare workers, only 21 provided informed consent to participate in the study. Out of 100 patients admitted from June 1 to October 1, four patients gave informed consent and were included. The decision to take HCQ as treatment or prophylaxis was based on hospital policy and various ongoing experimental treatments by the infectious disease department at our hospital. Once the patient had been decided to take HCQ, we asked them to participate in our study and took the willing patients. Twenty-five people were recruited: 20 healthcare workers and one patient for pre-exposure prophylaxis, and four patients with COVID who were treated with HCQ.

The mean age was 42.4 ± 14.1 years; 40% (10) were female, 8% (2) had hypertension, 4% (1) dyslipidemia, and no case of diabetes or coronary artery disease [Table 1].

Baseline mean QTc was 423.96 ± 32.18 ms, mean QTc corrected at 24 h was 438.93 ± 3 7.95 (P = 1.5), mean QTc was 451.879 ± 37.99 at 48 h (P = 2.8), and change from baseline mean QTc to maximum QTc was 30.74 ± 21.75 ms at 48 h [Table 2]. HCQ was stopped in four patients because of QT prolongation. All significant QTc prolongations were seen in the first 48 h of therapy and subsided in 3 days. When significant QTc was noted, subjects were admitted and monitored till the correction of QTc to normal values and removing and correcting other causes of QTc if present. No episode of TDP or malignant ventricular arrhythmia was noted. One medical student had one episode of accelerated idioventricular rhythm, and one had a short AF run. Other supraventricular arrhythmias were not noted. Few premature atrial complexes (APC) and ventricular premature complex (VPC) within the normal range were noted in study participants [Table 3].

All subjects developing QTc prolongation were greater than 50 years of age as compared to none in the younger age group. Two were hypertensive. Most of the prolongation of QTc

Table 1: Baseline characteristics

Parameter	Value
Age (years) (mean±SD)	42.4±14.1
Females	40% (10)
Hypertension	8% (2)
Diabetes	Nil
HCQ alone	96% (24)
HCQ + Azithromycin	4% (1)

HCQ=Hydroxychloroquine, SD=Standard deviation

Table 2: QTc Prolongation Trend

	QTc (Mean±SD) ms
Baseline	423.96±32.18
QT c 24 h	438.93±37.95
QT c 48 h	451.879±37.99
Change QT c	30.74±21.75

QTc=Corrected QT interval, SD=Standard deviation

Table 3: Arrhythmias and alerts

	n=25
QT >500 ms	16% (4)
Ventricular tachycardia	Nil
Ventricular Fibrillation	Nil
Junctional Rhythm	Nil
Pause >2 s	8% (2)
Asystole	Nil
Torse de pointais	Nil
PVC (>1%)	Nil
APC (>1%)	Nil
Atrial Fibrillation	4% (1)
AIVR	4% (1)
NSVT	4% (1)
VT/VF	Nil

QTc=Corrected QT interval, PVC=Premature ventricular ectopic, APC=Trail premature complex, AIVR=Accelerated idiot ventricular rhythm, NSVT=Non sustained ventricular tachycardia

occurred within 48–72 h and reverted within the next 48–72 h on stopping the medication.

Discussion

Indian Council of Medical Research (ICMR) Recommendations for electrocardiographic (ECG) monitoring for healthcare workers on HCQ prophylaxis is that an ECG (with the estimation of QT interval) may be done before prescribing HCQ prophylaxis. In case any new cardiovascular symptoms (e.g., palpitations, chest pain syncope) occur during prophylaxis, an ECG (with the estimation of QT interval) may be done in those who are already on HCQ prophylaxis before continuing it beyond 8 weeks. One ECG should be done anytime during prophylaxis.[6] There can be severe adverse events in following this protocol.

Cardiac telemetry can detect early QT prolongation and help in timely stopping the drug and taking preventive measures. In the elderly, hypertensive and those on diuretics or concomitant use of QT-prolonging drugs may have more risk of QT prolongation and should be monitored closely.[7] HCQ did not produce any episode of TDP, significant supraventricular, or ventricular arrhythmias if QT prolongation was detected early and further medication was stopped.

Previous studies have shown that HCQ and chloroquine decreased the excitability and conductivity of atrial and ventricular myocardium, though to a lesser extent than quinine or quinidine.[8] A study of 28 patients taking 250 mg daily of chloroquine found that QTc interval increased from 363–388 ms to 372–392 ms.[8] However, due to the higher dose used in prophylaxis and treatment, we observed more QTc prolongation. A study of 72 subjects with and without structural heart disease given acute chloroquine and HCQ therapy for various types of atrial and ventricular arrhythmias observed one sudden death.[9]

HCQ/chloroquine-induced TDP and ventricular tachycardia (VT) have been reported.[10,11] A trial administering high doses of chloroquine (600 mg twice daily) in conjunction with azithromycin in suspected cases of severe COVID-19 pneumonia was stopped due to excessive QTc prolongation and association with increased mortality.[11] Therefore, precautionary measures are necessary to mitigate the risk of QTc prolongation.[12] In a recent pharmacovigilance study, the use of HCQ was associated with cardiac arrhythmias and cardiomyopathy.[13] In all previous studies on ECG, there can be sudden deaths, and continuous mobile telemetry with alerts and beat-to-beat reports transmitted to physicians through satellite-based transmission is important to prevent sudden cardiac death. Monitoring methods that capture a full-disclosure ECG signal for every heartbeat provide a complete picture of a patient's arrhythmia activity and seem to be more protective than just ECG done at baseline and once a two or in a three-day schedule.

Intermittent ECG versus continuous telemetry

Drugs with the potential to further prolong QT should be avoided in patients with QTc greater than 500 ms (or 550 ms with intraventricular conduction delay), especially in the setting of moderate to severe structural heart disease and patients with high-grade atrioventricular block without a pacemaker and/or implantable cardioverter-defibrillator in place.[14,15] In our study, we found the incidence of QTc prolongation to be >500 ms only in people greater than 50 years of age. The incidence was more in hypertensive and on concomitant QTc prolonging drugs. A 54-year-old hypertensive female on olmesartan 20 mg, amlodipine 5 mg, and hydrochlorothiazide (HTZ) 12.5 mg once daily took HCQ prophylaxis. Her baseline QTc was 431 ms calculated by Bazzet's formula. Her baseline serum potassium was 4.1 meq/L. After receiving 400 mg HCQ, the QTc on telemetry was 490 ms [Figure 1a], and after receiving two doses of HCQ 400 mg and antihypertensive medications, QTc increased to 530 ms [Figure 1b]. Blood investigations showed serum potassium of 3.48 meq/L and serum magnesium of 2.08 meq/L. She was admitted for continuous cardiac rhythm monitoring. The Tisdale score calculated for the patient was 8, indicative of moderate risk of drug-induced QT prolongation.

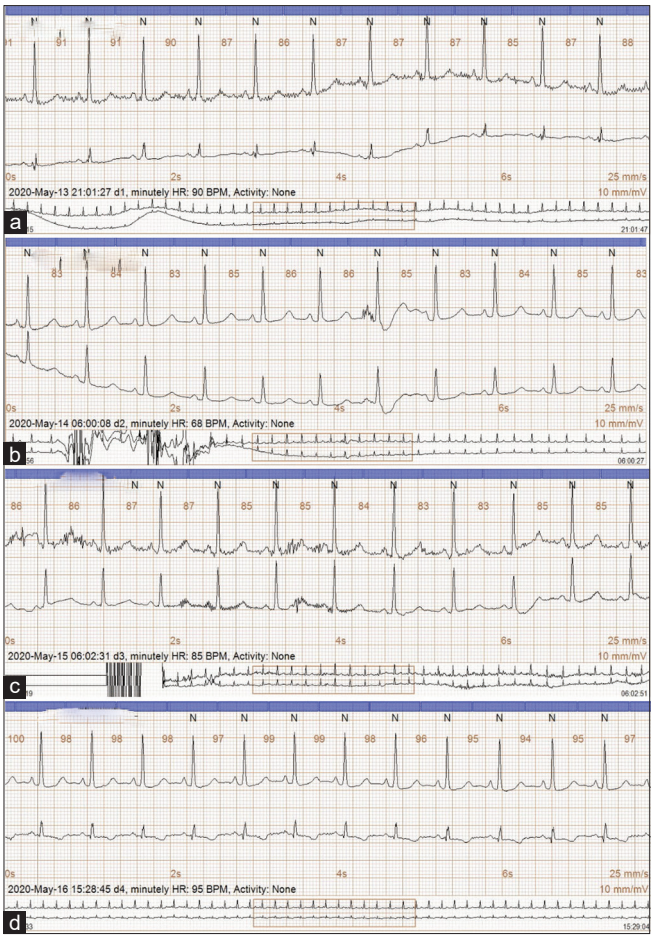

Figure 1: (a) Telemetry ECG strip taken after receiving one dose of HCQ 400 mg showing a heart rate of 90 bpm, QT interval of 400 ms, and QTc interval by Bazzet's formula of 490 ms. (b) Telemetry ECG strip after taking two doses of HCQ 400 mg and one dose of HTZ 12.5 mg showing a heart rate of 84 bpm, QT interval of 448 ms, and QTc interval by Bazzet's formula of 530 ms. (c) Telemetry ECG strip 24 h after 2nd dose of HCQ showing a heart rate of 85 bpm, QT interval of 430 ms, and QTc interval by Bazzet's formula of 512 ms. (d) Telemetry ECG strip after 57 h of 2nd dose of HCQ showing a heart rate of 95 bpm, QT interval of 360 ms, and QTc interval by Bazzet's formula of 453 ms.

HCQ and HTZ were stopped as both have a tendency for QTc prolongation. Potassium and magnesium replacement was started. Continuous cardiac monitoring can detect occasional ventricular premature complexes (VPC), but no polymorphic ventricular tachycardia (PVT) was detected, and the patient remained asymptomatic. Twenty-four hours after the second dose of HCQ, the QTc was still 512 ms [Figure 1c]. Regular monitoring of serum potassium and serum magnesium was done, which showed an improving trend. After 57 h of receiving the 2nd HCQ dose, the serum potassium was 4.5 meq/L, serum magnesium was 2.56 meq/L, and telemetry showed a QTc of 453 ms [Figure 1d]. The patient was discharged on oral magnesium salts and a high potassium diet, with the withdrawal of HCQ and HTZ from her medical regimen. Single nucleotide polymorphism may influence HTZ-induced hypokalemia, hypomagnesemia, and QTc prolongation.[16] The Tisdale score is a tool to predict the risk of QTc prolongation in patients on QTc prolonging drugs. A Tisdale score of ≤6 predicts low risk, 7–10 medium risk, and ≥11 high risks of drug-associated QT prolongation.[2]

QTc should be monitored closely

a. in patients with HCQ. If QTc increases by >60 ms or absolute QTc >500 ms (or >530–550 ms if QRS >120 ms), reduce the dose of HCQ and repeat ECG daily.
b. If QTc remains increased >60 ms and/or absolute QTc >500 ms (or >530–550 ms if QRS >120 ms), the physician should assess the risk/benefit of ongoing therapy or discontinuation of the drug.[2]

We found in our study that beat-to-beat telemetry-based ambulatory monitoring was better than intermittent ECG.

Duration of telemetry and risk

All subjects developing QTc prolongation were greater than 50 years of age than none in the younger age group. Two were hypertensive. Most of the prolongation of QTc occurred within 48–72 h and reverted within the next 48–72 h on stopping a medication. Careful monitoring until QTc is corrected, which may take 72 h, should be done.

COVID 19 and telemetry

Mobile-based ambulatory telemetry seems ideal in detecting dangerous QTc prolongation and taking timely measures to prevent sudden cardiac death. The study shows the value of ambulatory electrocardiographic monitoring for drug-induced arrhythmia. Because a vast number of drugs can induce QTc prolongation, which has a possibility of inducing TDP and can cause sudden cardiac death, primary and family physicians need to know and anticipate the arrhythmogenic properties of drugs and monitor QT in high-risk groups when these drugs are prescribed. Ambulatory electrocardiographic monitoring helps in QTc monitoring round the clock and early warning of dangerous prolongation of QTc.

Limitations

The study limitations are the single-centre, non-randomized study design and mostly a healthy population from a cardiac standpoint.

Conclusion

Ambulatory continuous beat-to-beat telemetry seems advantageous in detecting timely and early changes in QTc interval to dangerous levels and preventing sudden death. The risk of QTc prolongation and arrhythmia is low in the young population over 7 days. Ambulatory telemetry can be extremely valuable in the present COVID-19 pandemic and other conditions where numerous new experimental drugs that can prolong QTc are being used and cause malignant arrhythmias.

Key Points and Message

1. Ambulatory continuous beat-to-beat ECG telemetry is the ideal solution for arrhythmic drug monitoring for adverse

events such as QT prolongation and arrhythmias.
2. It helps in the early detection of ECG changes and can help take early preventive measures and initiate treatment.

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Conflicts of interest

There are no conflicts of interest.

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