Diabetes mellitus and QTc prolonging medications usage increased the risk of QTc prolongation during long-term hydroxychloroquine use- A databank based retrospective cohort study

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Abstract

Abstract Background Hydroxychloroquine plays a role in antimalaria, immune modulation, and possible novel coronavirus-2019 activity in vitro. The unwanted effect on QT prolongation could lead to lethal arrhythmia. Recently, American College of Cardiology (ACC) had announced to use a risk score system while treating patients with hydroxychloroquine. In this study, we investigated the possible risk factors of corrected QT (QTc) prolongation and validated the applicability of ACC risk score system in our cohort. Methods We retrospectively enrolled 4568 patients who had undergone long-term hydroxychloroquine. 167 patients had electrocardiography before and during hydroxychloroquine use. All baseline characteristics, laboratory data, comorbidities, and concurrent medications were all recorded. Results The majority (80.8%) of our cohort were female and the average age was 51.4 years old. The most common indication of hydroxychloroquine is an autoimmune disease (95.2%), and the average dosage was 315mg daily. In multivariable logistic regression, diabetes mellitus (OR, 9.286, 95% CI=2.026-45.22) and additional QTc prolonging medications (OR, 2.89, 95% CI=1.40-5.94) were stronger independent risk factors than ACC risk score (OR, 1.20, 95% CI=1.02-1.41) for QTc prolongation[?]60 ms. In linear regression, comorbidities and QTc prolonging medications (Adjusted R2: 0.385) provided more accurate prediction of QTc response than the ACC risk score alone (Adjusted R2: 0.259). Conclusions For those patients with long-term hydroxychloroquine use, patients with DM and additional QTc prolonging medications were more susceptible to significant QTc prolongation. Patient's baseline QTc interval, concurrent medications and comorbidities, rather than the ACC risk score, could be used to predict the response of QTc.

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Abstract

Background

Hydroxychloroquine plays a role in antimalaria, immune modulation, and possible novel anti-SARS-CoV activity in vitro. The unwanted effect on QT prolongation could lead to lethal arrhythmia. Recently, American College of Cardiology (ACC) had announced to use an ACC risk score system while treating patients with hydroxychloroquine. In this study, we investigated the possible risk factors of corrected QT (QTc) prolongation in patients with long-term hydroxychloroquine use and validated the applicability of ACC risk score system in this cohort.

Methods

We retrospectively enrolled 4568 patients who had undergone long-term hydroxychloroquine. Only 167 patients had electrocardiography before and during hydroxychloroquine use. All baseline characteristics, laboratory data, comorbidities, and concurrent medications were all recorded.

Results

The majority (80.8%) of our cohort were female and the average age was 51.4 years old. The prevalence of diabetes mellitus (DM) and hypertension were 20.4% and 54.5%. Furthermore, 37%, 10.2%, and 15% of the cohort had chronic kidney disease, atrial fibrillation, and congestive heart failure. Some patients had cancer (16.2%) and a history of sepsis (15.6%), respectively. The most common indication of hydroxychloroquine is an autoimmune disease (95.2%), and the average dosage was 315mg daily. In multivariable logistic regression, DM (OR, 9.286, 95% CI=2.026-45.22) and additional QTc prolonging medications (OR, 2.89, 95% CI=1.40-5.94) were independent risk factors for QTc prolongation>60 ms. ACC risk score was an independent but weaker risk factor (OR, 1.20, 95% CI=1.02-1.41). While long-term hydroxychloroquine use, comorbidities and QTc prolonging medications (Adjusted R^2: 0.385) provided more accurate prediction of QTc response than the ACC risk score alone (Adjusted R^2: 0.259).

Conclusions

For those patients with long-term hydroxychloroquine use, patients with DM and additional QTc prolonging medications were more susceptible to significant QTc prolongation. Patient's baseline QTc interval, concurrent medications and comorbidities, rather than the ACC risk score, could be used to predict the response of QTc after hydroxychloroquine therapy.

Key words: hydroxychloroquine; QTc interval; diabetes mellitus; risk score; electrocardiograms

Background

Quinidine is known intimately as a class Ia antiarrhythmic medication based on Vaughan Williams classification system, which exerts discrepant effects to block the fast sodium current and rapidly activating delayed rectifier potassium current (IKr). The latter effect leads to QT prolongation and risk of Torsade de pointes (TdP). Compared with procainamide and disopyramide, quinidine brings more risk of QT prolongation and TdP (1.5-8% per person-year)[1]. Instead of treating paroxysmal atrial fibrillation and idiopathic ventricular arrhythmias, quinidine nowadays contributes to suppression of ventricular arrhythmias in patients with Brugada syndrome and early repolarization syndrome by blockade of transient outward current (Ito)[2,3].

Hydroxychloroquine is structurally and electrophysiologically similar to quinidine[4]. It also plays a role as antimalarial drug, immunomodulation agents for autoimmune diseases and even recent novel therapy for COVID-19[5,6].

Since the end of 2019, an emerging infectious disease COVID-19 causes global health crisis with pandemic status announced by the world health organization (WHO). One pilot study in France showed that the hydroxychloroquine could reduce viral loads in a small series of COVID-19 patients[7]. More recently, one observational study in New York reported some conflicting results by the hydroxychloroquine treatment[8], and another registry study also showed that hydroxychloroquine or chloroquine were associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias while treating patients with COVID-19[9]. Regardless of the efficacy of hydroxychloroquine on COVID-19 patients, the safety of quinidine use should not be ignored, especially the side effect of QT prolongation and proarrhythmia[10]. Unexpected death had been reported because of arbitrary use of quinidine by those without guidance. To treat COVID-19 patients with quinidine, electrocardiograms (ECG) monitor and QTc surveillance is recommended by experts. The use a risk score to predict QT prolongation and adjust the treatment is also recommended by the American College of Cardiology (ACC)[11,12].

Nevertheless, it is still crucial to acknowledge the prevalence of such a lethal side effect before initiation of this novel therapy for COVID-19 patients with a specific region and race. Therefore, to understand the effect of long-term usage of quinidine in Asians, we performed this retrospective cohort study in a tertiary referral medical center, Tainan, Taiwan. Patients were recruited for analysis if they were treated with quinidine and received electrocardiography study before and after the therapy between 2009-2019. Our objective was to clarify the prevalence, characteristics and risk factors of QT prolongation in patients treated with long-term quinidine. In addition, we also tried to validate the feasibility of ACC risk score of QT prolongation proposed by Tisdale J et al.[12] in our patients.

Methods

Databank

We conducted a retrospective cohort study by using Cardiovascular Disease Databank (CDD) in National Cheng Kung University (NCKU) Hospital, which included the complete electronic medical records including patients' longitudinal data on demographics, symptoms, laboratory data, medications and image studies in out-patient department and hospitalization. This study was approved in our hospital by an independent ethics committee.

Study cohort

From January 1st, 2009 to December 31st, 2019, 4568 patients aged over 18 who were prescribed hydroxychloroquine were enrolled. The date of inclusion was defined as the date of first prescription within the cohort period. Those patients without ECG either before or after the prescription were excluded. Finally, 167 patients were enrolled for analysis (Figure 1). We followed-up these patients from the start-day of hydroxychloroquine therapy until the end of the study period or death, whatever came first.

To clarify the risk factors for significant QTc prolongation, patients were divided into two groups. Those patients with delta QTc[**?**]60ms (QTc after hydroxychloroquine minus baseline ECG) was considered as more susceptible to hydroxychloroquine.

Patients' characteristics and risk factors of QTc prolongation

Patient's baseline characteristics and possible risk factors of QTc prolongation were documented at the date of enrollment. To ensure the realness of patient's diagnosis, each variable was determined comprehensively based on the diagnosis of doctor's manual input, laboratory results, corresponding treatment and International Classification of Diseases (ICD) code (Supplemental Table 1).

One physician (Y. Liao) reviewed all the patient's electronic medical records and documented the dosage of hydroxychloroquine, indication of medication prescription, and cause of mortality. Furthermore, we

calculated the ACC risk scores (the range of risk score: 0-21 points) of QTc prolongation for each patient and divided them into low ([?]6 points), moderate (7-10 points) and high ([?]11 points) risk based on a previous study[12].

Electrocardiograms study

At least one ECG before and after the prescription of hydroxychloroquine should be documented on each patient. The QT interval was calculated and corrected for patient's heart rate using Bazett's formula (QTc) by Philips Electrocardiogram Machine (Koninklijke Philips N.V., Eindhoven, The Netherlands) automatically. The QTc value was represented by the median of all 12 ECG leads. Patients were ascertained to be prescribed hydroxychloroquine at the timing of follow up ECG after the date of enrollment.

Statistical analysis

We reported the overall number of eligible patients with hydroxychloroquine therapy and ECG document. Categorical variables were presented as frequencies and percentages, whereas continuous variables were reported as means and standard deviations. Box and whisker plots were used to display the distribution of both before-and after QTc prolongation. A paired t-test was performed to examine the overall change of QTc after hydroxychloroquine therapy. To clarify the association between QTc prolongation and corresponding risk factors, categorical data were compared using aχ^2 test or Fisher exact test and continuous variables were compared with Student's t test preliminarily. Then, risk factors were analyzed via univariate and multivariate logistic regression. Regression coefficients and odds ratio (OR) were calculated for each independent risk factor.

In addition, we performed univariate and multiple linear regression to predict the QTc response with corresponding risk factors, using forward selection to find the most fitting model. All statistical tests were 2-sided, and a P -value less than 0.05 was considered statistically significant. All analyses were performed using statistical software R 3.6.3 for Windows

Results

Demographic analysis of study cohort

Among 167 patients, 80.8% were female and the average age was 51.4 years old. The prevalence of diabetes mellitus (DM) and hypertension (HTN) were 20.4% and 54.5%. Furthermore, 37%, 10.2%, and 15% of the cohort had chronic kidney disease (CKD), atrial fibrillation (AF), and congestive heart failure (CHF). Some patients had cancer (16.2%) and a history of sepsis (15.6%), respectively. Most of the patients (95.2%) were treated with hydroxychloroquine for autoimmune diseases and the average dosage was 315mg daily (ranged from 200mg per week to 400mg twice per day). Regarding the QTc prolong drug, the most often prescribed medication was fluoroquinolones (33.8%), followed by class III anti-arrhythmic drug (20%) and anti-psychotics (20%). At the end of study period, twenty-six patients died. Only one death was documented to be contributed to ventricular arrhythmias.

Risk factors for significant QTc prolongation

All patients had two separate ECGs documents before and at the timing of ongoing hydroxychloroquine therapy. The average duration of hydroxychloroquine use was 133.1 days. Ninety-five patients were found QTc prolongation (delta QTc >0ms) after hydroxychloroquine therapy. Paired t test did no showed significant QTc change after hydroxychloroquine therapy (P =0.140, Figure 2). Nine patients had significant QTc change (delta QTc[?]60 ms) while another 158 patients did not. The baseline demographics of two groups of patients were shown in Table 1.

Univariable logistic regression indicated that patients with DM, AF, cancer or multiple QTc prolong medications were more susceptible to significant QTc change. In multivariable logistic regression analysis, only DM (OR, 9.55, 95% CI=2.02-45.22) and multiple QTc prolong medications (OR, 2.89, 95% CI=1.40-5.94) were associated with significant QTc prolongation (Table 2).

The average ACC risk score of the study group was 5.29 (ranged from 0 to 19). One hundred and eighteen, 30, and 19 patients were classified as low, moderate and high risk, respectively.After adjustment for other confounders, higher ACC risk score was still associated with significant QTc prolongation (OR=1.20, 95% CI=1.02-1.41, Table 2).

QTc response prediction

Multiple linear regression was used to construct a model to predict the QTc response (Table 3). Notably, using common comorbidities including QT prolonging medications, DM, HTN, and AF as explanatory variables (adjusted R^2 =0.385), model 4 provided more accurate prediction than using ACC risk score alone (model 1, adjusted R^2 =0.259).

Discussion

In this study, patients with long-term hydroxychloroquine therapy were examined for interval change of QTc. No significant QTc prolongation was observed overall during 221 days of average follow up period. Those patients with DM and QTc prolong medications were more susceptible to significant QTc prolongation. In multivariate logistic regression, ACC QTc risk score promoted by Tisdale et al.[12] was still associated with significant QTc prolongation in our patient group.

It should be noticed that patients' characteristics of the two groups were different. First, most of the patients in Tisdale's study group were admitted to cardiac care unit with continuously monitoring system due to cardiovascular emergency, while our patients were mainly followed up for autoimmune or dermatologic disease at out-patient department stably. Considering the majority of COVID-19 patients or other patients indicated for long-term hydroxychloroquine, they had mild illness. Our cohort may be suggestive to observe the QTc response after taking hydroxychloroquine before it was widely used. Second, only one patient in Tisdale's study group (derivation group) took quinidine. To clarify the practicality of the ACC risk score in our group, we did not count hydroxychloroquine initially as an QTc prolong drug in the analysis. In multiple linear regression analysis, QTc interval during hydroxychloroquine therapy could be more accurately predicted by taking patient's comorbidities into consideration (R^2=0.385) than ACC risk score alone (R^2=0.259, Table 3).

Dosage of hydroxychloroquine did not appear to be an independent factor for significant QTc prolongation in this study. In fact, the effective therapeutic dose of hydroxychloroquine for COVID-19 had not been well validated. A PK-QTc model proposed by Maria Garcia-Cremade et al. suggests a hydroxychloroquine doses more than 600 mg twice daily were predicted to prolong QTc intervals[13]. Since consensus guideline recommended a regimen of 400 mg twice daily loading dose followed by 200 mg daily for 4 days for COVID-19 patients[14], identifying those patients with additional risk factors for QTc prolongation during hydroxychloroquine use remained a more important issue.

The result that DM was a decisive factor for QTc prolongation was interesting but also compatible with findings of previous studies[15-18]. Glycemic variability increased the risks of QTc prolongation and dispersion in both type 1 and type 2 diabetic patients[15,16]. Cardiac autonomic neuropathy and reduced insulin sensitivity had also been reported to be associated with QTc prolongation in type 2 DM patients[17,18]. Of more interest, among type 1 DM patients, Suys et al. demonstrated a negative correlation between hourly mean QTc and interstitial glucose concentration[19], while Robinson et al. induced an acquired long QT syndrome during experimental hypoglycemia[20]. Insulin-induced hypokalemia and adrenergic stimulation were proposed to be the possible mechanisms of QTc prolongation in type 1 DM patients. Recently, hydroxychloroquine was found to be beneficial for glucose and lipid metabolism in DM patients[21,22]. From this viewpoint, we should suggest reevaluating the risk of QTc prolongation while better glycemic control was pursued.

Intuitively, concurrent use of other QTc prolong drugs was another independent factor of significant QTc prolongation. Among those patients with significant QTc prolongation, class III anti-arrhythmic drug was the most often prescribed QTc prolong drug in this study. One study describing the drug interaction between amiodarone and hydroxychloroquine in the literature[23]. Six patients were prescribed erythromycin

or erythromycin analog and hydroxychloroquine simultaneously, in which only one patient had significant QTc prolongation. The safety of concurrent use of azithromycin and hydroxychloroquine to treat COVID-19 patients was unfathomed in this study.

Study limitation

This retrospective study has several limitations. First of all, only a few patients were recruited for analysis after exclusion of those patients without ECG study before or during hydroxychloroquine therapy. Secondary, we adopt those factors and medications which were considered to be associated with QTc prolongation based on previous literatures. Confounding variables may be unrecognized and affect the results of analysis. Finally, patients were presumed to take all the medications in the electronic medical record. In real world, issue of patients' adherence always exists.

Conclusion

For those patients with long-term hydroxychloroquine use, patients with DM and their additional QTc prolonging medications were more susceptible to significant QTc prolongation. In summary, patient's baseline QTc interval, current medications and comorbidities (DM, AF, and HTN) were useful in predicting the response of QTc after hydroxychloroquine therapy.

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Figure legend

Figure 1. Flowchart of patient enrollment reagrding the effect of long-term hydroxychloroquine use in association with QTc prolongation on their EKGs.

Figure 2. Long-term use of hydroxychloroquine did not prolong the QTc duration. (A): individual point inidcated case before (Red dots) and after (Green dots) therapy; (B): paried dots indicated individuals with QTc duration before (Red dot) till after (Green dot) the therapy, which was connected by a line.

Figure 1.

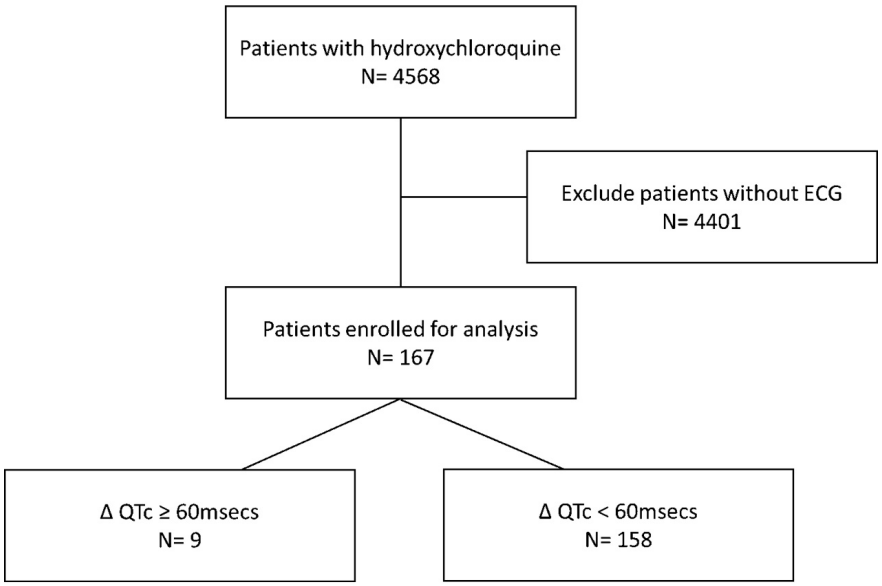

Figure 2.

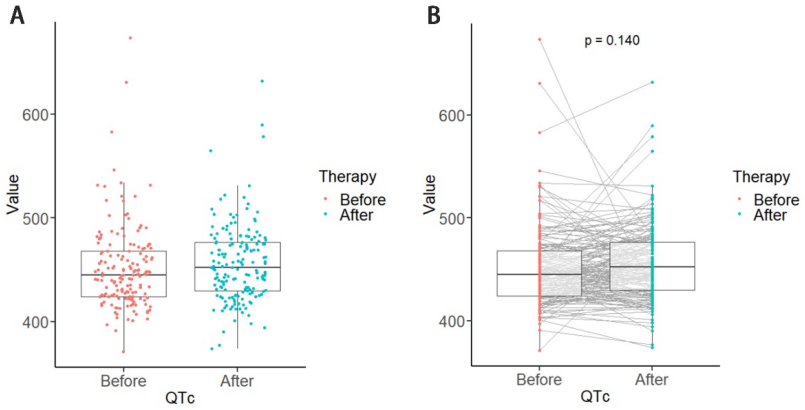

Table 1. Baseline Characteristics of Study Cohort Taking Long-term Hydroxychloroquine Seperated by the ΔQTc duration (<60 ms or not)

	ΔXTς<60 μς (N=158)	**ΔXTς[;]60 μς (N=9)**	*P*-value
	Mean (sd) / N (%)	**Mean (sd) / N (%)**	
Age(y)	51.19 (17.94)	56.60 (19.54)	0.382
Male	29 (18.4)	3 (33.3)	0.500
Death	21 (13.3)	5 (55.6)	0.003*
Body Mass Index (kg/mˆ2)	23.45 (5.01)	21.92 (2.14)	0.392

	ΔXTς<60 μς (N=158)	**ΔXTς[;]60 μς (N=9)**	***P*-value**
Dosage of hydroxychloroquine (mg)	315.91 (112.87)	311.11 (105.41)	0.901
Duration of hydroxychloroquine (days)	133.94 (106.54)	119.11 (72.82)	0.577
DM	28 (17.7)	6 (66.7)	0.002*
Dyslipidemia	75 (47.5)	6 (66.7)	0.437
HTN	83 (52.5)	8 (88.9)	0.074
CKD	33 (20.9)	4 (44.4)	0.214
AF	14 (8.9)	3 (33.3)	0.073
CHF	23 (14.6)	2 (22.2)	0.883
Cancer	23 (14.6)	4 (44.4)	0.057
Sepsis	23 (14.6)	3 (33.3)	0.299
Diuretics use	30 (19.0)	3 (33.3)	0.535
K^+	3.62 (0.61)	3.33 (0.46)	0.222
QT prolonging drug	0.39 (0.71)	1.44 (1.51)	<0.001*
Risk score	5.12 (3.89)	8.22 (3.56)	0.021*

Abbreviation: AF, atrial fibrillation; CHF, congestive heart failure; CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension

Table 2. Risk factors for significant QTc prolongation

Univariate analysis	**Variable**	**OR (95 % CI)**	***P* value**
	DM	9.28 (2.19, 39.38)	0.003 **
	AF	5.14 (1.16, 22.83)	0.031 *
	Cancer	4.70 (1.17, 18.80)	0.030 *
	QTc prolonging drug	2.82 (1.50, 5.30)	0.001 **
	Risk score	1.17 (1.02, 1.35)	0.028 *
Multivariate analysis			
Model 1	DM	9.55 (2.02, 45.22)	0.005 **
	QTc prolonging drug	2.89 (1.40, 5.94)	0.004 **
Model 2	DM	10.03 (2.22, 45.34)	0.003 **
	Risk score	1.20 (1.02, 1.41)	0.030 *

Abbreviation: AF, atrial fibrillation; DM, diabetes mellitus

Table 3 Prediction of QTc response during hydroxychloroquine use

	Variable	**coef. (sd)**	***P* value**	**Adjust R^2**
Model 1	Constants	340.33 (30.70)	< 0.001 ***	0.259
	Baseline QTc	0.22 (0.07)	0.003 ***	
	risk Score	3.46 (0.73)	< 0.001 ***	
Model 2	Constants	330.22 (29.78)	< 0.001 ***	0.309
	Baseline QTc	0.23 (0.07)	0.001 **	
	risk Score	3.24 (0.71)	< 0.001 ***	

	Variable	coef. (sd)	P value	Adjust R^2
	DM	21.51 (5.99)	< 0.001 ***	
Model 3	Constants	336.70 (29.06)	< 0.001 ***	0.345
	Baseline QTc	0.22 (0.07)	0.002 **	
	risk Score	2.66 (0.71)	< 0.001 ***	
	DM	20.37 (5.84)	< 0.001 ***	
	AF	26.01 (8.20)	0.002 **	
Model 4	Constants	330.01 (27.02)	< 0.001 ***	0.385
	Baseline QTc	0.24 (0.06)	< 0.001 ***	
	QTc prolong drug	13.59 (3.08)	< 0.001 ***	
	DM	17.85 (5.74)	0.002 **	
	AF	23.59 (8.02)	0.004 **	
	HTN	12.48 (4.75)	0.009 **	

* P < 0.1; ** P < 0.05; *** P < 0.01

Abbreviation: AF, atrial fibrillation; DM, diabetes mellitus; HTN, hypertension

Supplemental Table 1

	Definitions
Hypertension (HTN)	Documented in medical records of outpatient department or discharge note and/or co
Diabetes mellitus (DM)	Documented in medical records of outpatient department or discharge note and/or Hb
Hyperlipidemia	Documented in medical records of outpatient department or discharge note and or cor
Chronic kidney disease (CKD)	Documented in medical records of outpatient department or discharge note and/or eG
Cancer	Documented in medical records of outpatient department or discharge note
Sepsis	Documented in medical records of outpatient department or discharge note and/or ba
Diuretics	Use of Furosemide, burinex, spirolactone, trichlomethiazide, indapamide, mannitol, m
QTc prolonging drugs	Class III antiarrhythmia medications (amiodarone, sotalol), antibiotics (erythromycin