QTc-interval prolongation and increased risk of sudden cardiac death associated with hydroxychloroquine

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Aims: Hydroxychloroquine and chloroquine ([hydroxy]chloroquine) are drugs used to treat malaria and rheumatological disorders and were recently suggested as beneficial for prevention and treatment of patients with coronavirus disease 2019 (COVID-19) due to SARS-CoV-2 infection. However, longitudinal studies to assess the electrocardiographic and cardiotoxic effects of these drugs are limited. In this study, we aimed to investigate the effect of these drugs on QTc-interval and incidence of sudden cardiac death (SCD).

Methods: We designed a longitudinal follow-up study of individuals within the prospective population-based Rotterdam Study. Eligible individuals had available data on medication and repeated ECG measurements. The study period was between 1 January 1991 and 1 January 2014. We studied on current and past use of [hydroxy]chloroquine as a time-varying exposure; high versus low daily dose of [hydroxy]chloroquine. QTc-interval duration, and the occurrence of SCD were the main outcomes. SCD was defined as an unexpected and sudden death due to cardiac arrhythmia within one hour of the onset of acute symptoms, and in patients without cardiac symptoms within 24 hours before death.

Results: Among the study population of 14,594 individuals (58.8% women) with an average age of 65 years, 346 patients used [hydroxy]chloroquine at any time during follow-up. The total number of SCD cases was 609. In a multiple linear mixed model analysis, the current use of [hydroxy]chloroquine was associated with a significantly increased duration of the QTc-interval of 8.1 ms (95% CI: 3.6; 12.6) compared with non-users. The association was stronger among current-high daily dosage [15.3 (95%CI: 7.0; 23.6)] compared with current-low daily dosage [5.5 (95%CI: 0.4; 10.7)] users. In a Cox proportional hazard regression analysis, the risk of SCD was significantly higher in participants who were current users of [hydroxy]chloroquine than in non-users [adjusted hazard ratio; 3.7 (95%CI: 1.1; 12.6)].

Conclusions: In this longitudinal study, persons who received [hydroxy]chloroquine had an increased QTc-interval duration and the association was dose-dependent. [Hydroxy]chloroquine was associated with a significantly increased risk of SCD. As long as their activity against COVID-19 is controversial, cardiotoxicity is a strong argument against using these drugs to treat COVID-19 infections.

Keywords: Hydroxychloroquine • Chloroquine • Sudden cardiac death • QT/QTc-interval

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Introduction

Hydroxychloroquine and chloroquine ([hydroxy]chloroquine) are antimalarial drugs that are also used to treat immune-mediated disorders such as rheumatoid arthritis and systemic lupus erythematosus (SLE). They were recently suggested as potential, but controversial, therapies for patients with coronavirus disease 2019 (COVID-19). Although myocardial toxicity is uncommon, cardiomyopathy related to [hydroxy]chloroquine therapy is a severe complication that often leads to death. However, given the effect of confounding factors such as heart failure attributed to autoimmune diseases and hypertension, a causal relationship with direct myocardial toxicity is difficult to assess.

[Hydroxy]chloroquine inhibits voltage-gated sodium and potassium channels on heart muscle cells, which leads to prolongation of the QTc-interval. This reflects delayed cardiac repolarization which is a risk factor for sudden cardiac death (SCD). Despite that in an observational study involving patients with COVID-19 admitted to the hospital, hydroxychloroquine use was not associated with mortality, recent clinical trials that started treating COVID-19 patients with [hydroxy]chloroquine were halted due to increased risk of arrhythmia and mortality. In a recent randomized, controlled, open-label platform trial, in patients hospitalized with COVID-19, researchers randomly assigned 1561 patients to receive hydroxychloroquine and 3155 to receive usual care. The results of this study suggest that the mortality rate among patients in the hydroxychloroquine group was not lower than those who received usual care.

Longitudinal studies to assess the electrocardiographic and cardiotoxic effects of [hydroxy]chloroquine are limited. Given that the risk of SCD associated with [hydroxy]chloroquine has never been studied on a population-based scale and because the value of these drugs against COVID-19 infections is still inconclusive, we investigated the association between [hydroxy]chloroquine and QTc-interval duration and SCD in a population-based prospective cohort study.

Methods

Setting

This study is embedded within the framework of the Rotterdam Study, a prospective population-based cohort study among people ≥40 years of age living in the well-defined Ommoord district of Rotterdam, the Netherlands. Initially, in 1990, all inhabitants aged 55 years or over (n = 10 215) were invited to participate of whom 78% agreed. In 2000, out of 4472 invitees, 3011 participants who had reached the age of 55 years were invited to participate in the second cohort. In 2006, a third cohort included 3932 (out of 6057 invited) inhabitants aged 45 years and older with the total study population being 14 926 individuals by the end of 2008 (overall participation 72%).

The participants were all extensively examined at study entry i.e. baseline and subsequent follow-up visits that take place every 3–6 years. They were interviewed at home and then underwent an extensive set of examinations e.g. echocardiogram, echocardiography, computed tomography-scanning, and magnetic resonance imaging with an emphasis on imaging (of heart, blood vessels, eyes, skeleton, and later brain) and on collecting biospecimens that enabled further in-depth molecular and genetic analyses. The participants in the Rotterdam Study are followed for a variety of diseases that are frequent in the elderly, which include coronary heart disease, heart failure, and stroke, dementia, but also several other chronic diseases. Almost all the participants provided written informed consent to participate in this study. The Rotterdam study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare, and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The complete design of the Rotterdam Study has been described in a separate publication.

Study population

This study included participants from the first examinations of the first (1989–92), the second (2000–01), and the third (2006–08) cohorts. We included participants if they had information on medication data with at least one baseline interview or clinical examination. We excluded participants with ECGs recorded while on other QTc-prolonging medication use (n = 1183). Participants who later withdrew informed consent for the collection of follow-up data (n = 313) were also excluded from the analyses. The population for SCD assessment in this study consisted of 14 594 participants from the three cohorts. Data on repeated ECG measurements were available in 11 936 subjects. Figure 1 shows the flowchart of the study population.
Sudden cardiac death was defined as an unexpected and sudden death due to cardiac arrhythmia that occurs within 1 h of the onset of acute symptoms, and in patients within 24 h of not being symptomatic. The adjudication of SCD cases in the Rotterdam Study was performed by two physicians and ascertained by a cardiologist as described in detail previously.17

Statistical analysis

Descriptive analyses were performed by reporting mean [standard deviation (SD)] or median [interquartile range (IQR)] for continuous variables and numbers (with percentage) for categorical variables.

We assessed the ECG parameters in patients on current, and past [hydroxy]chloroquine use and compared the results with those in non-users. Since each subject had up to a maximum of five ECGs recorded, which are correlated in the same person, we performed a repeated measurement analysis applying a linear mixed model. The analyses were also stratified by sex, given different cut-off points of prolonged QTc in women and men (in women the cut-off points of ≤450 ms as standard, 451–470 ms as borderline, and >470 ms as prolonged, and in men, ≤430 ms as standard, 431–450 ms as borderline, and >450 ms as prolonged).18

We also studied the association between [hydroxy]chloroquine use and the risk of SCD, we used a Cox proportional hazard model. In all analyses, [hydroxy]chloroquine was analysed as a time-dependent variable,19 and past use (discontinuation) was a separate exposure category. In this way, every participant’s total follow-up time was distinguished into non-use, current use, and past use.

Because the elimination half-life can be very long due to lysosomal storage, we performed a sensitivity analysis with [hydroxy]chloroquine use with a cut-off of 250 days (five times the half-life in blood, in which the total amount of [hydroxy]chloroquine would normally be reduced by 97%).

In a sensitivity analysis, the association was further adjusted for baseline QTc-interval above the cut-off of >450 ms in men and >470 ms in women.

All analyses were adjusted for age and sex, baseline measurements of BMI, T2D, heart failure, myocardial infarction, hypertension, smoking behaviour, lipid-lowering drugs, and the average number of prescriptions until the occurrence of the outcomes.

We checked the proportional hazards assumption by plotting partial residuals. A two-sided P-value <0.05 was considered statistically significant. Imputation was performed using expectation-maximization, a single imputation method to impute the missing values. Data were analysed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics of the study population (n = 14,594) are shown in Table 1. In total, 346 patients used [hydroxy]chloroquine at any time during the study period. Mean age and median BMI were significantly higher among non-users (65.3 and 26.3) compared with [hydroxy]chloroquine users (62.1 and 26.0), respectively.
A total of 26,974 ECGs in 82% of individuals (n = 11,936) were recorded. Over a median (IQR) follow-up time of 10.4 (6.3–15.4) years, the number of SCD cases was 609 with a cumulative incidence rate of 4.2%.

The association of [hydroxy]chloroquine use and the risk of increased QTc-interval duration

Seven out of 77 ECGs (9.1%) recorded in 66 patients currently treated with [hydroxy]chloroquine had an increased QTc-interval duration; three were women with QTc-interval duration of 470 ms or greater, and four were men with QTc-interval duration of 450 ms or greater. The mean QTc-interval duration for the reference group was 428.469 ms. The association of current [hydroxy]chloroquine resulted in a significantly increased risk of SCD even after adjustment for age, sex, BMI, hypertension, smoking behaviour, lipid-lowering drugs, and the average number of prescriptions until the occurrence of SCD [multivariable model adjusted hazard ratio (HR), 3.7 (95% CI: 1.1; 12.6)] but not in past users [1.7 (95% CI: 0.97; 2.9)]. After adjustment for baseline QTc-interval above the cut-off, the HR did not change; HR of 3.8 (95% CI: 1.1; 12.8).

When choosing the cut-off of 250 days, the association between current hydroxychloroquine (n = 5) and the risk of SCD was slightly stronger; HR of 4.0 (95% CI: 1.3; 11.8).

Discussion

In this large prospective and population-based cohort study, current use of [hydroxy]chloroquine was associated with a significantly increased duration of the QTc-interval while this was not observed in past users. More importantly, the association was dose-dependent in which the higher dose, the higher the mean QTc-interval. Similarly, there was a significantly increased risk of SCD in current users but not in past users. Although the majority of participants used [hydroxy]chloroquine because of rheumatoid arthritis—a potential risk factor for cardiovascular disease—to this suggests that

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**Table 1  Baseline characteristics of the study populations**

|                                | Total (14,594) | [hydroxy]chloroquine users (n = 346) | [hydroxy]chloroquine non-users (n = 14,248) | P-value  |
|--------------------------------|----------------|--------------------------------------|------------------------------------------|---------|
| Age (years), mean (SD)         | 65.3 (10.3)    | 62.1 (7.1)                           | 65.3 (10.4)                               | <0.001  |
| Sex, women, n (%)              | 8580 (58.8)    | 209 (60.4)                           | 8371 (58.8)                               | 0.54    |
| BMI (kg/m²), median (IQR)      | 26.3 (24.4–28.8)| 26.0 (24.0–28.3)                     | 26.3 (24.4–28.2)                         | 0.02    |
| Hypertension, n (%)            | 7194 (49.3)    | 173 (50.0)                           | 7021 (49.3)                               | 0.79    |
| Total cholesterol (mmol/L), median (IQR) | 5.7 (5.0–6.4) | 5.6 (5.03–6.2)                      | 5.7 (5.0–6.4)                            | 0.08    |
| HDL cholesterol (mmol/L), median (IQR) | 1.3 (1.1–1.6) | 1.3 (1.1–1.6)                      | 1.3 (1.1–1.6)                            | 0.94    |
| Lipid-lowering medication, n (%) | 5167 (35.4)   | 94 (27.2)                            | 5073 (35.6)                              | 0.001   |
| Glucose (mmol/L), median (IQR) | 5.50 (5.1–6.0) | 5.5 (5.1–6.0)                        | 5.5 (5.1–6.0)                            | 0.55    |
| Type 2 diabetes, n (%)         | 1411 (9.6)     | 34 (9.8)                             | 1377 (9.7)                               | 0.46    |
| Myocardial infarction, n (%)   | 473 (3.2)      | 8 (2.3)                              | 465 (3.3)                                | 0.18    |
| Heart failure, n (%)           | 267 (1.8)      | 5 (1.4)                              | 262 (1.8)                                | 0.41    |
| Smoking status, ever, n (%)    | 7685 (52.6)    | 217 (62.7)                           | 7468 (52.4)                              | 0.15    |
| QTc-interval (ms), median (IQR)| 431.7 (418.9–423.3) | 430.2 (417.8–440.0)                | 431.7 (418.9–443.3)                     | 0.07    |
| Follow-up (years), median (IQR)| 10.4 (6.3–15.4) | 13.1 (7.2–20.7)                   | 10.2 (6.3–15.3)                          | <0.001  |

CVD, cardiovascular disease; HDL, high-density lipoprotein; IQR, interquartile range; SD, standard deviation.
**Figure 2** Association between [hydroxy]chloroquine and the mean QTc-interval duration. ECG, Electrocardiogram measurements; LCI, lower confidence interval; UCL, upper confidence interval. Adjusted for age, sex, body mass index, hypertension, type 2 diabetes, myocardial infarction, heart failure, smoking behaviour, and lipid-lowering drugs.

**Figure 3** Association between [hydroxy]chloroquine use dose categories and the mean QTc-interval duration. Low dosage: $\leq$0.3 DDD. High dosage: $>$0.3 DDD. Hydroxychloroquine DDD = 520 mg. Chloroquine DDD = 500 mg. ECG, electrocardiogram measurements; LCI, lower confidence interval; UCL, upper confidence interval. Adjusted for age, sex, body mass index, hypertension, type 2 diabetes, myocardial infarction, heart failure, smoking behaviour, and lipid-lowering drugs.
[hydroxy]chloroquine played at least a modifying role. A clinically relevant QTc-interval prolongation, a well-known risk factor for SCD, was observed in almost 9% of ECGs recorded in patients currently treated with [hydroxy]chloroquine. Also, several case-reports of cardiomyopathy attributed to [hydroxy]chloroquine itself have been published.²¹–²³

So far, [hydroxy]chloroquine has been given to thousands of individuals to prevent or treat the COVID-19 pandemic worldwide, although the efficacy is controversial. In an animal study, both in vitro and SARS-CoV-2-infected animals, evaluating the antiviral activity of hydroxychloroquine alone or in combination with azithromycin compared with the placebo, no significant difference was shown on viral load levels.²⁴ Moreover, this study revealed no preventive effect of [hydroxy]chloroquine, possibly because [hydroxy]chloroquine targets a pathway that is not operative in lung cells.²⁵ According to the FDA’s most updated review comments, hydroxychloroquine and chloroquine are potential causes of cardiac toxicities, including QTc prolongation, ventricular arrhythmias, torsade de Pointes (TdP), and conduction disorders.

Both hydroxychloroquine and chloroquine have a long elimination half-life of 40–50 days.¹²,¹³ Long-term treatment with [hydroxy]-chloroquine increases lysosomal dysfunction that impairs intracellular degradation processes and eventually accumulates glycogen and phospholipids as metabolic products.¹¹,²⁶–²⁸ Toxicity associated with [hydroxy]chloroquine could occur within the recommended daily dosages, but plasma levels do not help in understanding the underlying mechanism.²⁶,²⁹ The structure of [hydroxy]chloroquine is similar to the class IA antiarrhythmic quinidine that inhibits voltage-gated sodium and potassium channels. Several different risk factors are known to induce drug-associated QT/QTc prolongation, such as female gender, heart disease, electrolyte disturbances, diabetes, concomitant use of QT/QTc-interval-prolonging medications, and genetic factors that cause QTc-interval prolongation and affect myocardial depolarization and repolarization.³⁰ Given the risk of cardiac adverse effects, these drugs should be used with caution in individuals with known risk factors such as heart disease, a family history of SCD, and notably in patients who are already taking QT/QTc-interval-prolonging medications.

Although the association between QT-prolongation and SCD in population-based studies gave conflicting results,³¹,³² prolonged QTc-interval is considered a potential mediating factor in triggering TdP. Torsade de Pointes is a potentially life-threatening tachyarrhythmia which often leads to ventricular fibrillation and SCD. However, the effect of QTc-interval prolongation on TdP and eventually SCD is not straightforward. A QT/QTc-interval above 500 ms has been associated with a higher risk of TdP and SCD. However, SCD can also occur in individuals with QT/QTc-intervals within the normal range. Nevertheless, QT/QTc-interval prolongation is still considered a surrogate marker of increased risk of SCD.³²,³³

**Strengths and limitations**

Our study’s strength is its prospective cohort design and long follow-up and the fact that we had precise and detailed pharmacy-based filling data available at the time of ECG or death, as well as access to up
to five recorded ECGs per individual over a relatively long follow-up. This enabled us to obtain more precise ECG measures along with [hydroxy]chloroquine use. Furthermore, the risk of selection or information bias is unlikely as the SCD cases were ascertained without prior knowledge of this study hypothesis. However, our study also has some limitations, such as the small number of cases of SCD currently exposed to [hydroxy]chloroquine. A second limitation is that we did not have data on the indication for use in the currently exposed cases of SCD. However, during the repeated drug interviews, almost all participants stated that they used these drugs for a rheumatic disorder or SLE. Confounding by indication cannot be ruled out, but the fact that past users no longer had an increased risk argues against confounding by indication.

Conclusions

Patients who received [hydroxy]chloroquine during a follow-up time of almost 10 years experienced increased QTc-interval duration, and the risk of SCD was higher in this population. Although further longitudinal studies may be warranted to confirm our results, it seems that the widespread use of [hydroxy]chloroquine to treat COVID-19 infections with a high burden of cardiovascular disease—as propagated by some—should be discouraged until unequivocal proof of the drug efficacy is delivered.

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Data sharing statement

We are not planning to disseminate our results to the study participants.

Conflict of interest: all authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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