State of the art paper

Hydroxychloroquine, QTc prolongation and risk of torsades de pointes

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Abstract

Hydroxychloroquine (HCQ) is a common medication used for the treatment of rheumatic diseases. As a result of its widespread use during COVID-19, there are increasing concerns about its cardiotoxicity. HCQ is known to cause QTc prolongation, and its long-term use has been associated with cardiomyopathy and conduction abnormalities. Despite reports of ventricular arrhythmia in COVID-19 patients taking HCQ, there have been reassuring data in approved indications. HCQ has been in use for several decades with a good safety profile. In addition to better disease control and prevention of flares, it is associated with decreased risk of cardiovascular diseases. But given its small risk of cardiotoxicity, clinicians should be aware of this effect and monitor patients for developing cardiac symptoms.

Key words: hydroxychloroquine, cardiotoxicity, QTc prolongation, torsades de pointes, COVID-19.

Introduction

Hydroxychloroquine (HCQ) is a disease-modifying antirheumatic drug (DMARD) that is commonly used for the treatment of systemic lupus erythematosus (SLE) and early rheumatoid arthritis (RA) with mild to moderate disease [1]. It has been in use for more than 60 years, since 1955 [2]. In early 2020, there was a significant increase in its use as a potential treatment and post-exposure prophylaxis for COVID-19. Randomized controlled trials showed no clinical benefit of its use in the setting of COVID-19 [3–5] but this widespread use highlighted its role in QTc prolongation and its arrhythmogenic potential, prompting the US Food and Drug Administration (FDA) [6], the Centers for Disease Control and Prevention [7], and the American Heart Association [8] to issue warnings regarding fatal cardiac toxicity from ventricular arrhythmias, particularly torsades de pointes (Tdp). The FDA revoked the emergency use authorization to use HCQ for the treatment and prevention of COVID-19 in June 2020 based on the results of these randomized controlled trials [6].

Hydroxychloroquine

Hydroxychloroquine is a widely used medication in the treatment of rheumatic diseases. In addition to SLE and RA, it has been effective in the

treatment of juvenile idiopathic arthritis, discoid lupus, and skin rash of dermatomyositis along with other rheumatic indications [1].

The recommended dosage for these indications is 200 to 400 mg/day (less than or equal to 6.5 mg/kg ideal body weight of HCQ base) [1].

HCQ is a weak base and accumulates in acidic lysosomes and increases lysosomal pH, causing a disruption in the normal assimilation of peptides with class II major histocompatibility complex (MHC) molecules or binding of RNA/DNA to toll-like receptors. It has also been shown to decrease production of interleukin-1 (IL-1), IL-6, interferons and prostaglandins by cells [1].

Adverse effects of HCQ include cutaneous (hyperpigmentation), musculoskeletal (myopathy), retinal toxicity, and cardiovascular toxicities [1]. Acute cardiovascular toxicities manifest as QTc interval prolongation with rare reports of torsades. Long term use of HCQ has been found to be associated with increased risk of developing cardiomyopathy and conduction abnormalities [9, 10].

QTc interval

The QT interval is the time required for ventricular depolarization and repolarization. It is measured from the beginning of the QRS complex to the end of the T wave and is corrected for heart rate, thus giving the corrected QT (QTc) interval. There are different formulas available; the Bazett formula is commonly used. The QTc interval (Bazett-corrected) is considered prolonged if > 450 ms in adult males and > 470 ms in adult females [11].

QTc prolongation is mainly caused by delayed repolarization. Outward K+ currents are mainly responsible for repolarization of ventricular myocytes. The major current is the delayed rectifier K+ current I_k, which consists of a rapidly and a slowly activating component (I_{kr} and I_{ks}). Antimalarial drugs are known to cause QT interval prolongation by blocking the rapidly activating delayed rectifier K+ current (I_{kr}), encoded by the human-ether-a-go-go-related gene (hERG) [12].

In addition to QTc prolonging medications, there are several other factors found to be associated with a prolonged QTc interval, including age, female gender, electrolyte abnormalities (hypokalemia, hypocalcemia), history of myocardial infarction, history of thyroid disease [13], high levels of anti-Ro antibodies [14], and congenital long QT syndromes [15].

QTc length is an important parameter as studies have shown that QTc prolongation significantly predicts all-cause mortality [16]. A study showed increased incidence of QTc prolongation among RA patients (48% at 20 years after RA occurrence) compared to non-RA patients (38% at 20 years after index date; $p = 0.004$) and it was marginally associated with all-cause mortality (HR = 1.28; 95% CI: 0.91–1.81, $p = 0.16$) [17]. It has been shown to be associated with risk of sudden cardiac death (SCD) in the general population and patients with coronary artery disease. Idiopathic abnormal QTc prolongation was associated with 5-fold increased odds of SCD (odds ratio = 5.53; 95% confidence interval: 3.20–9.57) [18]. A prolonged QTc interval was associated with a threefold increased risk of sudden cardiac death (hazard ratio = 2.5; 95% CI: 1.3–4.7), after adjustment for other factors [19].

Clinical evidence of QTc prolongation and torsades with HCQ use

Use in rheumatic diseases

It is well known that hydroxychloroquine can cause QT prolongation. Several studies have shown QTc prolongation with HCQ use in rheumatic diseases. However, most of the pre-COVID studies are case reports or smaller retrospective studies [20–23].

Nishiyama *et al.* grouped SLE patients based on whether they were treated with HCQ or not and change of QTc was measured and compared before and after HCQ administration with the control group. In the HCQ group, the mean QTc significantly increased ($p < 0.001$), while there was no significant difference of mean QTc in the control group. Moreover, those in the HCQ group with QTc prolongation showed a significantly higher proportion of hypertension and longer SLE duration compared to those without QTc prolongation. However, the multiple logistic regression analysis showed that there were no significant differences among them [24]. A retrospective study categorized patients into six cohorts based on exposure to hydroxychloroquine, methotrexate, or sulfasalazine alone, or the combination of any of those drugs with any concomitant drug known to prolong the QT interval. A statistically significant increase in QTc interval of 18.0 ms (95% CI: 3.5–32.5; $p < 0.05$) was found in the hydroxychloroquine monotherapy cohort [25].

In the COVID-19 setting

Most of the recent studies conducted were in the setting of HCQ use in COVID-19. Cavalcanti *et al*. conducted a multi-center randomized, controlled trial including patients hospitalized with mild-to-moderate COVID-19. The results did not show improved clinical status as compared with standard care. Prolongation of QTc interval was more frequent in patients receiving HCQ alone or with azithromycin [26].

In a study conducted on COVID-19 positive patients in the ICU, 93% of the 40 studied patients

had an increase in QTc prolongation and 36% had critical QTc prolongation. Among patients treated with HCQ and azithromycin, 6 of 18 patients developed an increase in QTc of 500 or more [27]. A systemic review of the literature was conducted to estimate the risk of chloroquine and HCQ cardiac toxicity in COVID-19 patients. A total of 19 studies with a total of 5652 patients were included. The pooled incidence of torsades de pointes, ventricular tachycardia or cardiac arrest was 3 per 1000 (95% CI: 0–21) [28]. Sridhar *et al.* studied 111 patients with COVID-19 who underwent treatment with HCQ monotherapy; no episodes of sustained ventricular arrythmia or ventricular cardiac arrest were observed. Clinically significant QTc prolongation was seen in 7% of patients [29].

Data from studies involving COVID-19 patients may not be applied to patients taking HCQ for approved indications for several reasons. COVID-19 is a pro-arrhythmogenic state and may increase the risk of cardiotoxicity in the acute setting [30]. Also in most studies, HCQ was administered to patients with severe symptoms and to patients in intensive care units, increasing the risk of indication bias. HCQ was mostly administered along with other QTc prolonging medications, particularly azithromycin [31–33], and in higher doses compared to the doses given in rheumatic diseases [34].

Use with other QTc prolonging medications

An important question is the effect on QTc when HCQ is used along with other medications known to cause QTc prolongation. A study investigated QTc prolongation risk when hydroxychloroquine was administered along with 118 drugs using real-world data. A statistically significant interaction in the direction of QTc prolongation was found with 12 drugs (trimebutine, tacrolimus, tramadol, rosuvastatin, cyclosporin, sulfasalazine, rofecoxib, diltiazem, piperacillin/tazobactam, isoniazid, clarithromycin, and furosemide). In eight drugs (trimebutine, tramadol, rosuvastatin, cyclosporin, sulfasalazine, rofecoxib, diltiazem, and isoniazid), an interaction was present in the direction of increasing the risk of QT prolongation, even though the risk of QT prolongation was not observed with the use of those drugs alone. This interaction was explained by the effect of medications on the metabolism of HCQ through the CYP 450 pathway as most of these concomitant medications have inhibitory effects on the metabolic pathway, increasing the concentration of HCQ [35]. In a cohort study of 90 hospitalized patients with COVID-19, use of hydroxychloroquine with or without azithromycin for treatment of COVID-19 was associated with frequent QTc prolongation, and those taking hydroxychloroquine and azithromycin had greater QTc prolongation than those taking hydroxychloroquine alone. One patient developed torsades de pointes [31]. Similarly, Ramireddy *et al.* reported a significantly larger change in QTc from baseline to treatment in the HCQ and azithromycin group vs HCQ alone (17 ±39 ms vs. 0.5 ±40 ms; $p = 0.07$). More concerning, up to 12% of all patients in this study (receiving HCQ alone, azithromycin alone, or both) had critical QTc prolongation (defined as maximum QTc ≥ 500 ms (if QRS < 120 ms) or QTc ≥ 550 ms (if QRS ≥ 120 ms) and a QTc increase of ≥ 60 ms); however, no torsades de pointes was documented [32]. Padilla *et al.* found that in hospitalized COVID patients, concomitant exposure to hydroxychloroquine and azithromycin was significantly associated (HR = 11.28, 95% CI: 1.08–117.41) with prolongation of the QTc [33].

Reassuring data in approved indications

Other studies have shown that QTc prolongation is not of concern when used in approved indications of rheumatic diseases. In a combined cohort of SLE and RA patients without clinical cardiovascular disease (CVD), adjusted QTc length was comparable between HCQ and non-HCQ users (438 ms vs. 437 ms). A significant interaction was found between HCQ use and use of anti-psychotics. HCQ use combined with any QTc prolonging medication as a group was associated with a QTc length (434 ms; 95% CI: 430–439) which was comparable to that of use of HCQ alone (433 ms; 95% CI: 429–437) [36].

Sarayani *et al.* analyzed data from the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) (> 13 million total reports) for HCQ/chloroquine (CQ) alone, azithromycin alone, HCQ/CQ + azithromycin, and amoxicillin alone. HCQ was not associated with a safety signal related to torsades de pointes/QT prolongation or death when used alone in these approved indications, whereas azithromycin with or without HCQ was associated with QT prolongation [37].

In a cohort of SLE patients, there was no significant difference in mean QTc based on HCQ use. Patients with chronic kidney disease (CKD) were more likely to have prolonged QTc when compared to those without CKD, but there was no significant difference in mean QTc based on HCQ use as well in this subset. Severe prolongation of QTc was rare in all groups and no episodes of serious tachyarrhythmia or Tdp were observed [38]. Lane *et al.* reported *no increased risk* of cardiac arrhythmias (calibrated HR = 0.90; 95% CI: 0.78–1.03; $p < 0.01$) in HCQ users (400 mg/day for 30 days) vs. sulfasalazine users in a retrospective review of 14 multinational databases of RA patients [39]. In another prospective study of RA patients, the incidence of long QT syndrome or arrhythmia-related

hospitalizations was comparable between HCQ use vs non-HCQ DMARD use [40].

Cardioprotective role of HCQ

Rheumatic diseases including SLE and RA are found to be linked to increased risk of developing cardiovascular diseases. RA patients develop atherosclerosis 10 years earlier compared to patients who do not have RA but have the same traditional cardiovascular risk factors. The risk of coronary artery disease is increased 2-fold to 8-fold in SLE patients [41]. HCQ, by decreasing disease activity and better disease control, reduces that risk. It has been shown to have a role in lowering lipid level and preventing diabetes by increasing lipoprotein receptors and decreasing degradation of insulin respectively. Also it has a role in preventing thrombosis by inhibiting platelet aggregation and adhesion [1]. Studies have shown favorable effects of HCQ on coronary artery disease in patients with rheumatic diseases. Liu *et al.* reported a *lower* risk of CVD including sudden cardiac arrest/death in HCQ/chloroquine (CQ) users vs non-users (RR = 0.72; 95% CI: 0.56–0.94; $p = 0.013$) in a meta-analysis of various rheumatologic patients [42]. Other studies have shown lowered risk of coronary artery diseases, improved cardiovascular risk profile, decreased incidence of thrombosis, and improved lipid profile in patients taking HCQ for rheumatic diseases. Hung *et al.* found a decrease in risk of coronary artery disease in RA patients receiving HCQ [43]. Rempenault *et al*. in 2018 found that CQ and HCQ lowered CVD in rheumatic disease [44]. Mathieu *et al.* found that RA patients receiving HCQ had an improved cardiovascular risk profile compared to other RA patients [45]. Sharma *et al*. in 2016 found that HCQ receipt was associated with a 72% decrease in the risk of incident CVD in RA patients [46]. Van Halm *et al.* in 2006 found that HCQ reduced cardiac events in RA patients [47]. Yang *et al.* in 2019 found a decreased risk for coronary artery disease in patients with systemic lupus erythematosus receiving high doses of HCQ for at least 318 days [48]. Shapiro and Levy in 2017 found decreased mortality with HCQ. In 514 RA patients (241 patients receiving HCQ and 273 controls), the mortality rate for HCQ was 22.4%, versus 38.5% in the control arm. A total of 13.3% of HCQ patients receiving 400 mg/day experienced cardiovascular events compared to 38.1% in the control group [49].

Studies have reported a decreased incidence of thrombosis [50, 51] and a better lipid profile [52, 53] in patients receiving HCQ.

Future perspective

Most of the studies conducted in the pre-COVID era were case reports and small retrospective studies. There is a need for a larger prospective study to determine the role of HCQ in development of ventricular arrhythmias, particularly torsades, in the general population and in patients with existing risk factors.

The 2019 HCQ recommendations for EULAR only recommended screening for retinal toxicity in patients receiving HCQ for extended periods of time. There are no current guidelines for cardiac monitoring. However, clinicians can consider getting a baseline EKG in patients with additional risk factors for QTc prolongation as well as EKG at regular intervals if found to have prolonged QTc. Also, combining HCQ with other QTc prolonging medications should be avoided. As long-term use of HCQ has been associated with developing cardiomyopathy and conduction abnormalities, clinicians should monitor patients for developing cardiac symptoms when getting HCQ.

Executive summary

HCQ is a well-tolerated medication with a good safety profile when used in approved indications. It has been in use for more than 60 years and its importance in the treatment of rheumatic diseases cannot be denied. Several metabolic and cardiovascular benefits have been associated with its use. It has been found to reduce the risk of CVD, prevent thrombosis and improve lipid profile. Also there is a high risk of disease flare if discontinued.

HCQ is associated with QTc prolongation, and there have been rare reports of ventricular arrhythmias, particularly Tdp. However, most of the recent data were in the setting of HCQ use in COVID-19, which may not be extrapolated to patients taking it for autoimmune indications. There have been reassuring data in the setting of approved indications. Thus, in summary, the small risk of cardiotoxicity with HCQ use should be weighed against the well-known benefits of its use in rheumatic diseases.

Conflict of interest

The authors declare no conflict oif interest.

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