Hydroxychloroquine Is Protective To The Heart, Not Harmful: A Systematic Review

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Abstract

Background: Hydroxychloroquine (HCQ) has been shown to be at least somewhat effective in treating COVID 19 patients. Recently FDA and CDC warnings of fatal cardiac toxicity from Torsade de Pointes (TDP) arrhythmia from HCQ use have been made, notwithstanding the long safe HCQ use for lupus and rheumatoid arthritis. This has resulted in restricted access of HCQ for COVID 19 treatment. We hypothesized that HCQ and azithromycin have not been reported to cause significant acute cardiac arrhythmic mortality.

Methods: We performed a literature search for the effects of HCQ and azithromycin on the heart.

Results: No Torsade de Pointes or related deaths were found to have been reported as a result of HCQ and azithromycin use in the peer reviewed literature. To the contrary HCQ/azithromycin were uniformly found to substantially reduce cardiac mortality and also to decrease thrombosis, arrhythmia and cholesterol in treated patients in recent peer reviewed studies and meeting presentations.

Conclusions: HCQ and azithromycin do not cause TDP cardiac mortality but rather decrease it. HCQ should not be restricted in use for COVID 19 patients because of fear of cardiac mortality.

Introduction

Several clinical studies, now numbering thousands of patients, [1-4] have shown apparent substantial clinical benefit from the use of hydroxychloroquine (HCQ) in COVID 19 patients and have not reported adverse cardiac events. A number of meta-analyses [5-7] have also shown overall good results although with limited quality studies. Usage of HCQ would therefore be warranted for COVID 19 by physicians who were so inclined unless there were significant clinical risks to offset the apparent benefits.

However, recently numerous warnings have been issued from the FDA [8], CDC [9], the American Heart Association [10] and elsewhere about potential fatal cardiac toxicity from Torsade de Pointes or other ventricular arrhythmias from HCQ use. These warnings state that such fatalities could occur secondary to the increase in QTc that is sometimes seen with the use of HCQ as well as azithromycin, which is often used in combination with HCQ.

These warnings however seemed odd to us since HCQ has been used in millions of lupus, and rheumatoid arthritis patients for more than fifty years with a general reputation for safety. Practicing rheumatologists generally prescribe it without ordering a baseline EKG unless the patient has a history of cardiac disease. Furthermore, azithromycin is also regularly prescribed without a baseline EKG and is not generally felt to be cardiotoxic to patients with an otherwise normal heart.

These warnings have had the effect of restricting HCQ use to the hospital in some locales. This may not be consistent with good patient care since HCQ is known to be best applied earlier in the patient course before hospitalization. It has also resulted in some pharmacists refusing to fill HCQ prescriptions for COVID 19 thus restricting access to a potentially beneficial drug.

Thus it would be of great benefit to know whether there is in fact significant cardiac risk from the use of HCQ. We hypothesized that the scientific literature would not show clinical evidence of increased cardiac mortality from HCQ or HCQ plus azithromycin from Torsade de Pointes: ie that the reported potential cardiac "risk"[9] of cardiac mortality would not be accompanied by reports of "actual" TDP or other QTc related cardiac mortality.

Materials and Methods

We limited this study to HCQ and not chloroquine since chloroquine is more toxic than HCQ such that we do not believe chloroquine has a place in the treatment of COVID 19: particularly given the wide availability and low cost of HCQ.

We also excluded reports of HCQ cardiomyopathy. This is a rare condition that is only seen after many years, and usually decades, of use and thus is not relevant to the brief periods of time that HCQ is used to treat COVID 19. This cardiomyopathic damage is also not what is referenced by agencies that warn of HCQ cardiotoxicity, which rather refers to QTc prolongation and the risk of Torsade de Pointes.

We conducted a search of the Pubmed, Medline, Cochrane, Embase and Google Scholar databases. Search terms included hydroxychloroquine and azithromycin and the following co-search terms: cardiac, heart, arrhythmia, ventricular arrhythmia, Torsade de Pointes, COVID 19, treatment for COVID 19, mortality and death. We identified relevant articles. We included only articles which included clinical series, but searched systematic reviews to identify other clinical series. We identified 4 case reports [11, 12] of HCQ cardiomyopathy after long term use, which were excluded as explained above. The remaining papers were individually analyzed for evidence of cardiac morbidity and mortality.

Results

Overall our literature search found that, except for a few case reports of non-fatal adverse events, HCQ is actually consistently associated with a decreased incidence of cardiac adverse events and no cardiac mortality from Torsade de Pointes.

Non-Fatal Cardiac Adverse Event Case Reports

We found 3 case reports [13-15] of patients with increased QTc or other conduction block arrhythmia in patients with Lupus and 1 in a patient with COVID 19 [16]. However, in all cases the patients were successfully treated without any deaths occurring.

Non-Fatal Cardiac Adverse Event Clinical Series

We found 1 case series [17] of 251 COVID 19 patients treated with HCQ and azithromycin. 23% developed extreme QTc prolongation. However, HCQ was discontinued and no deaths occurred.

Cardiac Mortality from HCQ Induced TDP or Other Arrhythmia

None reported: We did not find any reports of a cardiac death from TDP or other arrhythmia from the use of HCQ.

Papers Showing a Decreased Incidence of Cardiac Events from the Use of HCQ

Eight papers showed a decreased incidence of CV disease in patients taking HCQ.
Hung [18]in 2018 stated "This study revealed association of decreased CAD risk in RA patients taking HCQ. The protective effect of HCQ on CAD is consistent regarding subgroup analysis on age, gender and different comorbidities groups." Liu [19] in a 2013 paper entitled "Chloroquine and hydroxychloroquine are associated with reduced cardiovascular risk: a systematic review and meta-analysis" found a lower risk of CVD in patients with rheumatic diseases who were using with HCQ or Chloroquine. Rempenault [20] in 2018 found that CQ and HCQ lower CVD in rheumatic disease from their study results. Mathieu [21] also in 2018 states "Our study results provide information that reinforces the conclusions of Rempenault *et al* that HCQ leads to an improvement in the cardiovascular risk profile in RA."
Sharma [22] in 2016 found that "hydroxychloroquine use was associated with a 72% decrease in the risk of incident CVD in RA patients." Van Halm [23] in 2018 found that HCQ reduced cardiac events in RA patients. Yang [24] in 2019 found that "After adjusting for chronic comorbidity, a significantly decreased hazard ratio (HR) for coronary artery disease (CAD) was found among SLE patients with a high usage of HCQ for at least 318 days." Shapiro [25] in 2017 found decreased mortality with HCQ. In 514 RA patients - 241 HCQ, 273 control – the mortality rate for HCQ was 22.4%, vs 38.5% in control. 13.3% of HCQ patients using 400mg/day suffered cardiovascular events compared with 38.1% in the control group. "The use of HCQ is independently associated with decreased risk for cardiovascular morbidity among RA patients, particularly when using the higher dose of 400 mg per day. This newly demonstrated effect of HCQ should be considered in the overall management of RA".
Neonatal Cardiac Lupus
Izmirly [26] in 2013 showed the recurrence rate of cardiac-Neonatal Lupus in fetuses exposed to HCQ was 7.5% (3/40) compared to 21.2% (46/217) in the unexposed group (p=0.050). While there were no deaths in the exposed group, the overall case fatality rate of the cardiac-NL fetuses in the unexposed group was 22%.
Atrial Fibrillation
Gupta [27] in 2018 showed a 67% decreased risk of atrial fibrillation in patients taking HCQ.
Thrombosis
3 papers [28-30] showed a decreased incidence of thrombosis in patients taking HCQ. Konig [29] in a 2019 study, presented at the American College of Rheumatology Annual Conference, found a lower incidence of thrombosis the higher the level of HCQ in the blood.
Cholesterol and Lipid Profile
Two papers [31, 32] showed lower cholesterol or lipid profile in patients taking HCQ.
Clinical Series Using HCQ in COVID 19
A clinical series [2] of 1061 COVID 19 patients treated with HCQ and azithromycin had 8 deaths. "All deaths resulted from respiratory failure and not from sudden death. All had repeated ECG with none showing Torsade de Pointes." They obtained a baseline EKG in all patients and discontinued HCQ when necessary. They have now treated over 4000 patients with no cardiac mortality.
Azithromycin
We found 5 reports of the cardiotoxicity of HCQ on COVID 19 patients. [17, 33-36]. All papers described increased "risk" of TDP or related ventricular arrhythmia. However in none of the 5 papers had an actual HCQ-AZ death actually occurred.

A report by Farkas [37], explained that HCQ is actually an anti-arrhythmic drug and that it has never been shown to predispose to TDP. Ohara further describes azithromycin has never been shown to cause TDP in a paper entitled, "Azithromycin Can Prolong QT Interval and Suppress Ventricular Contraction, but Will Not Induce Torsade de Pointes" [38]. In addition, azithromycin has been shown to improve cardiac remodeling and decrease heart failure after myocardial infarction [39].

Discussion

The most important finding of this review is that evidence shows HCQ to be overall significantly cardioprotective, and apparently not cardiotoxic in short term use. This supports our hypothesis that prudent use of HCQ would not cause significant mortality from Torsade de Pointes or related cardiac causes. This finding of cardioprotection, which was surprising to us, goes well beyond our hypothesis. Perhaps because many of the studies showing cardioprotection are relatively recent, the cardioprotective effect seems to be generally unknown to both the general population and the medical community. The cardio-protection includes a decrease in cardiac events, in thrombosis in general, in arrhythmia, in lipid profile and even in fetal disease. With HCQ generally beneficial to the heart in patients with rheumatic disease, there would be no reason to think that it would be cardiotoxic in COVID 19 patients, unless these patients were late in the disease course with established viral cardiac damage. Even then this would be only a theoretical risk because it is also possible that HCQ might be protective of further damage in this circumstance.

The second major finding of this study is that we were unable to find any reports of TDP death from HCQ induced TDP in the peer reviewed literature. This suggests that, in fact, no actual significant risk of TDP exists if HCQ is used prudently in accordance with established guidelines. In this regard, the protocol used by Didier Raoult's group [2] is instructive. They obtain a baseline EKG and serum electrolyte analysis before beginning HCQ. The EKG is repeated 48 hours after the start of treatment and HCQ is discontinued when the corrected QT interval is >500ms. Using this common sense protocol, they have now treated over 4000 patients without a single cardiac mortality. TDP may occasionally occur in association with HCQ use. But based on our finding of not a single mortality being reported in the peer reviewed literature, we believe that the frequency of HCQ associated TDP is extremely low and the incidence of subsequent TDP induced mortality caused by HCQ is rare if it exists at all. Anecdotally the the Department of Health and Human Services Pharmacovigilance Memorandum [40] which publishes self-reported adverse events from providers and patients reported 4 cases of TDP with 1 mortality from their entire database. The report is not peer reviewed. There is no way to verify the report itself, causality or whether appropriate procedures were followed. But at worst this would still represent only a single TDP mortality despite very widespread HCQ COVID-19 use.

The cardio-protective properties of HCQ should not be surprising. Cardiac events, including thrombosis are caused in part by inflammation. HCQ is an anti-inflammatory drug. Furthermore, its separately described anti-thrombotic properties would also be expected to be cardio-protective.

Limitations of this study include the possibility that cardiac deaths have occurred but not been reported. However, even if a small number of TDP deaths have occurred, it would not change the finding that HCQ is overall safe and generally beneficial for the heart.

In fact, the finding of an anti-thrombotic effect, an anti-arrhythmic effect, and a reduction in CVD events raises the possibility that HCQ should be considered in well controlled clinical trials as a treatment for COVID 19 patients who have sustained cardiac damage as a possible mitigant of these effects..

CONCLUSIONS

1. HCQ is apparently not dangerous to the heart and indeed is strongly cardioprotective. It results in a lower incidence of cardiac events as well as lower levels of arrhythmia, cholesterol, and thrombosis.
2. No TDP deaths from HCQ have apparently been reported in the peer reviewed literature. The potential risk of fatal arrhythmia, e.g. TDP, from HCQ, appears to be essentially a theoretical risk only. It appears to occur very rarely if ever in clinical practice if HCQ is used according to standard treatment protocols.
3. Current recommendations to use HCQ only in hospital are likely the opposite of what they should be. Instead of recommending HCQ for use in hospital for sicker patients later in their COVID course, HCQ should be recommended primarily early in treatment before hospitalization becomes necessary when HCQ is thought to be most effective for COVID 19.
4. Azithromycin used in combination with HCQ also appears to be quite safe, does not appear to cause TDP mortality, and is also apparently cardioprotective.
5. Due to its ability to decrease CVD events, decrease arrhythmia, decrease thrombosis and decrease cholesterol, HCQ should be considered as an agent for study to potentially treat patients who have developed cardiac damage from COVID 19.

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