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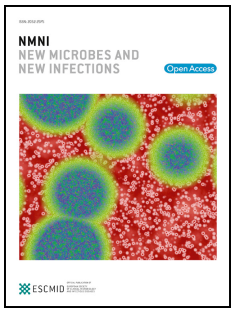

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Hydroxychloroquine Is Protective To The Heart, Not Harmful: A Systematic Review

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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. HCQ decreases cardiac events. 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. The FDA warning on reseased June 15th along with the revoking of it's prior emergency use authorization states that "Additionally, in light of ongoing serious cardiac adverse events and other potential serious side effects, the known and potential benefits of chloroquine and hydroxychloroquine no longer outweigh the known and potential risks for the authorized use"[11]. However this warning does not reference any specific study, or comment on if any deaths have occurred.

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[12]. Practicing rheumatologists generally prescribe it without ordering a baseline EKG unless the patient has a history of cardiac disease. The 2019 hydroxychloroquine reccomendations for the European League against rheumatology (EULAR) only mention

screening for retinal toxicity in patients on hydroxychloroquine for extended periods of time[12]. 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, or entire pharmacy boards[13] 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 clinical series including case reports, prospective and retrospective cohort studies, and meta-analyses. Due to the emerging nature of the COVID-19 pandemic we included pre-print papers in our analysis, including papers published on medRxiv (which are indexed in Google scholar). The last day of this search consultation was June 1st 2020. We identified 4 case reports [14, 15] 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.

Table 1. Literature Review Results on HCQ and Cardiac Events

Paper	Type of Study	# of Patients	HCQ dosage and regimen	HCQ duration	Associated medications	Comorbidities of patients/ cardiac background	Study findings
Morgan 2006 [16]	Case Report	1	200 mg twice daily	3 years	NA	41 year old female with CHF and left sventricular dysfunction. Also suffered from systemic lupus erythematosis and hypertiension. 3 years post reanal transplant	QTc prolongation
O'laughlin 2016 [17]	Case Report	1	200 mg daily	2 years	NA	50 year old female with history of SLE, ESRD on dialysis, and A-fib on anticoagulant	QTc prolongation
Chen 2006 [18]	Case Report	1	200 mg daily	1 year	15 mg prednisolone daily,200 mg daily teophyliine	67 year old famale with a history of SLE, liver cirrhosis and portal vein thrombosis, asthma, and old	Prolonged QTc leading to Torsades de Pointes

						myocardial infarct with ventricular septal defect	
Asli 2020 [19]	Case Report	1	400 mg stat dose, then 200 mg twice daily	3 days	initially amoxiciillin - clavuanic acid, switched to meropenem 1000 mg three times daily	60 year old female with history of hypertension hyperlipidemia, and overweight.	Right bundle branch block and prolonged QTc
Erkan 2002 [20]	Cross-sectional study	133 patients with antiphospholipid syndrome	NA	NA	NA	All patients with history of antiphospholipid sydnrome	Found a lower rate of thrombosis in aPL positive patients taking either aspirin or hydroxychloroquine
Izmirly 2012 [21]	Historical Cohort Study	40 neonates, whose mothers receiving HCQ prior to delivery	at least 200 mg daily	At lest prior to 10 weeks gestation	NA	Neonatal infants whose mothers previously gave birth to a child with cardiac neonatal lupus, or whose mother had anti-SSA/Ro and/or SSB/LA antibodies	Infants with mothers receiving hydroxychloroquine had a 64% lower chance to develop cardiac-neonatal lupus

Petri 1994 [22]	Longitudinal Cohort study	264 total patients, 125 patients using hydroxychloroquine	NA	NA	80% of all patients in study receiving prednisone	All patients with systemic lupus erythematosus	Found hydroxychloroquine use was associated with lower serum cholesterol levels.
Hung [23]	Population based retrospective cohort study	173 in HCQ group	NA	> 180 days	NA	Rheumatoid arthritis patients	Showed decreased risk of coronary artery disease in rheumatoid arthritis patients taking hydroxychloroquine
Konig 2020 [24]	Prospective Cohort study	812 patients	NA	NA	NA	All patients with systemic lupus erythematosus	HCQ blood levels inversely associated with risk of any thromboic event
Ruiz-Irastorza 2006 [25]	Prospective Cohort Study	104 HCQ patients	NA	average 52 months	NA	Study of 232 patients with systemic lupus erythematosus	Patients receiving either HCQ or chloroquine were less likely to have a thrombotic event
Rho 2009 [26]	Prospective Cohort study	169 total patients, 42 currently using either HCQ or Chloroquine	NA	NA	71% of all patients in the study receiving methotrexate	All patients with rheumatoid arthritis	Diastolic blood pressure, serum LDL and triglyceride levels were all lower in patients currently taking HCQ or chloroquine

Million 2020 [2]	Prospective Cohort Study	1061 patients	200 mg HCQ three times daily	10 days	500 mg azithromycin in day 1, followed by 250 mg daily day 2-5	Patients with PCR confirmed COVID-19	9 patients had QTc prolongation of more than 60 ms from baseline. No patient exceeded 500 ms QTc. No incidents of Torsades de Pointes.
Bun 2020 [27]	Prospective Cohort study	71 patients receiving HCQ	200 mg three dimes daily	10 days	Azithromycin 500 mg day 1, 250 mg day 2-5	All PCR confirmed COVID-19 patients	Significant QTc prolongation leading to stoppage of therapy in 2 patients. No incidences of drug induced life-threatening arrhythmias or death observed
Saleh 2020 [28]	Prospective observational study	201 total patients, 191 receiving HCQ	400 mg twice on day 1, then 200 mg twice daily for days 2-5.	5 days	119 patients also receiving Azithromycin- 500 mg daily for 5 days	All PCR confirmed COVID-19 patients	Patients with azithromycin had greater rates of QTc prolongation only discontinued in 3.5% of patients. No instances of Torsades de Pointes.
van Halm 2006 [29]	Retrospective Case Control Study	613 total patients usind DMARDs, 244 of these using HCQ	NA	NA	NA	NA	RA patients using DMARDS (including HCQ) reduce risk for cardiovascular disease

Sharma 2016 [30]	Retrospective Cohort study	547 HCQ patients	NA	average 2.3 years	NA	NA	Rheumatoid arthritis patients receiving HCQ showed 72% reduction in all CVD events.
Yang 2019 [31]	Retrospective Cohort Study	795 HCQ patients	NA	Variable, grouped from <105, 105-318, and >318	NA	Patients with prior history of cardiovascular disease excluded from study	Risk for coronary artery disease decreased in patients with high cumulative doses of HCQ (>100,267)
Shapiro 2016 [32]	Retrospective Cohort Study	241 HCQ patients	either 400 mg daily or 200 mg daily	NA	majority of patients also receiving Prednisone or methotrexate	NA	Patients receiving HCQ had lower risk of arterial and venous cardiovascular disease events
Gupta 2018 [33]	Retrospective Cohort Study	754 HCQ patients	NA	NA	NA	NA	lower risk of atrial fibrillation in patients using hydroxychloroquine
Mercuro 2020 [34]	Retrospective Cohort study	90	400 mg twice on day 1, then 400 mg daily for days 2-5.	5 days	53 patients also receiving Azithromycin	Patients with PCR confirmed COVID-19. Most patients had at least 1 cardiovascular comorbitidy.	7 patients developed prolong QTc of over 500 ms, and 3 patients had an increase in QTc of 50 ms or more. 1 Case of torsades de pointes reported

Hooks 2020 [35]	Retrospective Cohort Study	819 patients receiving HCQ	Median dosage 400 mg daily	median duration 1006 days	NA	All patients with rheumatic disease	12 patients with a QTc over 500 ms, average patient increased QTc by 7.6 ms on treatment. Average on-treatment QTc was 430.9 ms
Chorin 2020 [36]	Retrospective study	251	Loading dose of 400 mg twice for one day, then 200 mg twice daily	5 days	Azithromycin 500 mg daily for 5 days	NA	QTc > 500 ms in 23% of patients, one patient developed polymorphic ventricualr tachycardia (suspected as Torsades des Pointes)
Liu 2018 [37]	Systematic Review and Meta-Analysis	19,679 total patients	NA	NA	NA	NA	Hydroxychloroquine or chloroquine use was associated with a 30% reduction in the risk of cardiovascular disease in patients with rheumatic disease
Rempenault 2019 [38]	Systematic Review and Meta-Analysis	12,245 HCQ patients	NA	NA	NA	NA	Rheumatoid arthritis patients receiving HCQ showed modifiable risk factors for cardiovascular disease, including improved: lipid profile, diabetes

							incidence, HBA1C, and decreased cardiovascular events.
Mattieu 2018 [39]	Systematic review and meta-analysis	24,923 HCQ patients	NA	NA	NA	NA	Rheumatic disease patients treated with HCQ had a better cardiovascular disease risk profile and less cardiovascular events.

Non-Fatal Cardiac Adverse Event Case Reports

We found 3 case reports [16-18] of patients with increased QTc or other conduction block arrhythmia in patients with Lupus and 1 in a patient with COVID 19 [19]. 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 [36] of 251 COVID 19 patients treated with HCQ and azithromycin. 23% developed extreme QTc prolongation. However, HCQ was discontinued in patients with QTc prolongation 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 cardiovascular disease (CVD) in patients taking HCQ. Hung [23]in 2018 found a decrease in risk of coronary artery disease (CAD) in rheumatoid arthritis (RA) patients taking HCQ. Liu [37] found this protective effect of HCQ on CAD was applicable across a range of ages, different genders, and multiple co-morbidities 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 [38] in 2018 found that CQ and HCQ lower CVD in rheumatic disease from their study results. Mathieu [39] also in 2018 found that RA patients using hydroxychloroquine had an improved cardiovascular risk profile when compared to other RA patients.

Sharma [30] in 2016 found that hydroxychloroquine use was associated with a 72% decrease in the risk of incident CVD in RA patients. Van Halm [29] in 2018 found that HCQ reduced cardiac events in RA patients. Yang [31] in 2019 found a decreased risk for coronary arter disease in SLE patients with high dosage use of HCQ for at least 318 days. Shapiro [32] 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. They concluded that

HCQ use in RA patients was associated with decreased cardiovascular morbidity, especially in higher dosage HCQ patient of 400 mg per day.

Neonatal Cardiac Lupus

Izmirly [21] 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 [33] in 2018 showed a 67% decreased risk of atrial fibrillation in patients taking HCQ.

Thrombosis

3 papers [20, 24, 25] showed a decreased incidence of thrombosis in patients taking HCQ. Konig [24] 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 [22, 26] 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. However, all of these deaths were caused by respiratory failure from COVID-19, and no patients showed Torsades 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. [27, 28, 34-36]. All papers described increased "risk" of TDP or related ventricular arrhythmia. However, none of the 5 papers reported an actual HCQ-AZ death.

A report by Farkas [40], 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" [41]. In addition, azithromycin has been shown to improve cardiac remodeling and decrease heart failure after myocardial infarction in animal models [42].

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 [43] 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[44]. HCQ is an anti-inflammatory drug[45]. Furthermore, its separately described anti-thrombotic properties[46] 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

HCQ is apparently not dangerous to the heart and indeed is cardioprotective. It results in a lower incidence of cardiac events as well as lower levels of arrhythmia, cholesterol, and thrombosis. 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. Azithromycin used in combination with HCQ also appears to be safe, does not appear to cause TDP mortality, and is also apparently cardioprotective. 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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