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VIEWPOINTS

Chloroquine or Hydroxychloroquine for COVID-19: Is Cardiotoxicity a Concern?

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The severe acute respiratory syndrome coronavirus 2 viral pandemic causing coronavirus disease 2019 (COVID-19) begs for rapid and innovative treatments. While most patients have mild symptoms, some will become critically ill and are straining existing clinical resources in many places around the world. In addition to flu like symptoms, acute cardiac manifestations in hospitalized patients in Wuhan, China, included cardiac injury (7.2%), shock (8.7%), and arrhythmia (16.7%).[1]

Several pharmacological therapies have been suggested including repurposing of existing drugs such as chloroquine and hydroxychloroquine, which were first developed in the World War II era for treatment and prophylaxis of malaria. These drugs were developed before modern drug safety surveillance programs, including the recognition that some drugs can cause long QT syndrome and the ventricular arrhythmia torsades de pointes. The concept that chloroquine might be effective in treating COVID-19 viremia stems from in vitro work done during the severe acute respiratory syndrome era nearly 20 years ago. In February of this year, Chinese virologists reported that chloroquine and its less toxic derivative hydroxychloroquine could stop infection of severe acute respiratory syndrome coronavirus 2 in vitro.[2] Emerging clinical trials from China and France suggest potential benefit using chloroquine or hydroxychloroquine, sometimes combined with the macrolide antibiotic azithromycin, to treat acute COVID-19 patients resulting in more rapid reduction in viral shedding and possible improved clinical outcomes.[3,4] However, the available data are scant and far from conclusive at this point. There is growing interest in using these agents for treatment of acute COVID-19 as well as for prophylaxis, with clinical trials underway around the world including the United States (see ClincialTrials.gov). Given limited treatment options for COVID-19, off-label use of chloroquine and hydroxychloroquine, sometimes with azithromycin, is currently widespread. Besides drug shortages and limiting the availability of the drugs for patients relying on them for treatment of some rheumatological disorders, is there the potential for other unanticipated adverse consequences?

Chloroquine and hydroxychloroquine were recognized as impacting the electrophysiological properties of the heart decades ago. Clinically, they can prolong the QT interval that could potentially initiate ventricular arrhythmias including torsades de pointes. Chloroquine is known to be an open channel blocker of the hERG 1A and 1A/1B potassium channel that in the heart underlies the repolarizing potassium current I_{Kr}; chloroquine binds to the common drug-binding site in the channel pore. Block of I_{Kr} is the principal cause of drug-induced long QT syndrome. Chloroquine also binds to cardiac sodium, calcium, and inward rectifier potassium channels to potentially cause QRS widening and conduction abnormalities. In a recent review of cardiac complications attributed to long-term chloroquine or hydroxychloroquine use, cardiac conduction disorders and heart failure were the most common findings.[5] The drugs have active metabolites and have relatively long elimination half-lives—once given their drug effects and toxicities may take weeks to dissipate. In the Comprehensive In Vitro Proarrhythmia Assay initiative to develop approaches to test for drug-induced torsades de pointes

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risk, chloroquine was included as the control "nonbalanced," predominant hERG channel blocker, where it caused QT interval lengthening as well as mild PR and QRS widening.[6] Additionally, chloroquine has a relatively narrow therapeutic window, with multiple cases of overdose leading to death from hemodynamic collapse or ventricular arrhythmias, and lethal overdose has recently been observed during this pandemic. Nevertheless, over >6 decades of use and millions of patients, the incidence of unanticipated sudden cardiac death is rarely reported except in cases of severe overdose. While chloroquine and hydroxychloroquine are older drugs whose development preceded modern thorough QT testing, their ability to prolong the QT interval does not appear to be associated with a substantial risk of sudden cardiac death and torsades de pointes.[7] Despite this, caution is warranted in new applications using these drugs since most trials assessing their benefit did not study patients with cardiovascular comorbidities and disease where arrhythmia risk is the greatest.

Concern about azithromycin and increased cardiovascular death was raised in 2012 with the greatest risk in patients with underlying cardiovascular disease.[8] The US Food and Drug Administration recognized this. Azithromycin can cause modest QT interval prolongation, but not through potent hERG channel blockade, rather when used chronically through an increase in peak and late cardiac sodium current to cause potential loading of cardiomyocytes with sodium and calcium to produce calcium overload.[9]

How should we proceed with the use of chloroquine and hydroxychloroquine, potentially combined with azithromycin, for COVID-19 given that these agents bring some cardiac toxicity risk and their mechanisms for cardiac toxicity may not be the same? Is combining different and potentially additive mechanisms of cardiotoxicity wise? There are no available data from large randomized clinical trials defining dosing or duration of use for either prophylaxis or treatment of severe acute respiratory syndrome coronavirus 2 infection. Whether in clinical trials or for empiric off-label treatment, some patients are at higher risk of cardiac arrhythmic complications and likely should not be candidates for these drugs including patients with a prolonged QT interval, patients with known or suspected congenital long QT syndrome, patients receiving other QT interval–prolonging drugs, patients with marked electrolyte disorders (particularly low serum potassium), and possibly patients with significant, untreated conduction abnormalities. It is reasonable to obtain a baseline ECG before treatment whenever possible to exclude a prolonged QT interval or advanced conduction system disease. In addition, critically ill patients receiving treatment need to be monitored by telemetry to detect serious arrhythmias. Clinicians should be alert for the potential of proarrhythmia drug effects. Nevertheless, given the overall safety profile of these quinolones, one can anticipate relatively little cardiac toxicity for a short course in noncritically ill patients and in prophylactic uses in the absence of underlying cardiac disease. However, in critically ill COVID-19 patients, the risk of adverse cardiac events secondary to chloroquine and hydroxychloroquine is greater given the impact on the myocardium of cytokine storm from aggressive pulmonary infection as well as possible hypoxia in addition to the potential for viral myocarditis. How great the risk is relative to the benefit in critically ill patients with COVID-19 will need to await the outcome of ongoing, controlled clinical trials. The emerging treatments for COVID-19 require not only rapid implementation but thoughtful considerations to minimize unintended consequences including arrhythmias.

ARTICLE INFORMATION

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Disclosures
None.

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