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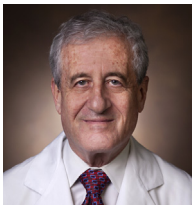


Considerations for Drug Interactions on QTc Interval in Exploratory COVID-19 Treatment

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Hydroxychloroquine and azithromycin have been touted for potential prophylaxis or treatment for patients with coronavirus disease 2019 (COVID-19). Both drugs are listed as definite causes of torsade de pointes at crediblemeds.org. There are occasional case reports of hydroxychloroquine's prolonging the QT interval and provoking torsade de pointes (1–4) when used to treat systemic lupus erythematosus. Antimalarial prophylactic drugs, such as hydroxychloroquine, are believed to act on the entry and post-entry stages of severe acute respiratory syndrome–associated coronavirus (SARS-CoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, likely via effects on endosomal pH and the resulting underglycosylation of angiotensin-converting enzyme 2 receptors that are required for viral entry (5).

The widely used antibiotic azithromycin is increasingly recognized as a rare cause of QT interval prolongation (6,7), serious arrhythmias (8,9), and increased risk for sudden death (10); advanced age and female sex have been implicated as risk factors. Interestingly, azithromycin can also provoke non-pause-dependent polymorphic ventricular tachycardia (11,12). A U.S. Food and Drug Administration perspective supported the observations that azithromycin administration leaves the patient vulnerable to corrected QT (QTc) interval prolongation and torsade de pointes (13).

Basic electrophysiological studies suggest that both drugs can provoke proarrhythmia via mechanisms beyond block of the rapidly activating delayed rectifier potassium current IKr implicated in usual cases of torsade de pointes (14,15). The effect of the combination of these agents on QT interval or arrhythmia risk has not been studied. There are very limited data evaluating the safety of combination therapy. Multiple randomized trials are currently being initiated.

Seriously ill patients often have comorbidities that can increase the risk for serious arrhythmias. These include hypokalemia, hypomagnesemia, fever (16), and an inflammatory state (17). Mechanisms to minimize arrhythmia risk include the following:

- Electrocardiographic/QT interval monitoring
  - Withhold the drugs in patients with baseline QT interval prolongation (e.g., QTc interval ≥500 ms) or with known congenital long-QT syndrome.
  - Monitor cardiac rhythm and QT interval, and withdraw the drugs if QTc interval exceeds a preset threshold of 500 ms.
  - In patients critically ill with COVID-19, frequent caregiver contact may need to be minimized, so

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TABLE 1 Torsade de Pointes Potential and Post-Marketing Adverse Events Associated With Possible COVID-19-Repurposed Pharmacotherapies

	CredibleMeds Classification	VT/VF/TdP/ LQTS in FAERS	Cardiac Arrest in FAERS
Repurposed antimalarial agents			
Chloroquine	Known risk	72	54
Hydroxychloroquine	Known risk	222	105
Repurposed antiviral agents			
Lopinavir/ritonavir	Possible risk	27	48
Adjunct agents			
Azithromycin	Known risk	396	251

Reproduced with permission from Giudicessi et al. (5).

COVID-19 = coronavirus disease 2019; FAERS = U.S. Food and Drug Administration Adverse Event Reporting System; LQTS = long-QT syndrome; TdP = torsade de pointes.

optimal electrocardiographic interval and rhythm monitoring may not be possible.

- Correction of hypokalemia to a level of >4 mEq/l and hypomagnesemia to a level of >2 mg/dl
- Avoidance of other QTc interval-prolonging agents (5) whenever feasible

Safety considerations for the use of hydroxychloroquine and azithromycin in clinical practice have been described (18).

Some of the current COVID-19-repurposed drugs are listed in **Table 1**.

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