

Considerations for Drug Interactions on QTc in Exploratory COVID-19 (Coronavirus Disease 2019) Treatment

Running Title: *Roden et al.; Drug Interactions on QTc in Exploratory COVID-19 Treatment*

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Hydroxychloroquine and azithromycin have been touted for potential prophylaxis or treatment for COVID-19 (coronavirus disease 2019) infection. Both drugs are listed as definite causes of torsade de pointes at crediblemeds.org. There are occasional case reports of hydroxychloroquine prolonging the QT interval and provoking torsade de pointes¹⁻⁴ 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 SARS-CoV (severe acute respiratory syndrome–associated coronavirus) and SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection, likely via effects on endosomal pH and the resulting under-glycosylation 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 prolongation,^{6,7} serious arrhythmias,^{8,9} and increased risk for sudden death¹⁰; advanced age and female sex have been implicated as risk factors. Interestingly, azithromycin can also provoke non-pause–dependent polymorphic ventricular tachycardia.^{11,12} The FDA *Perspective* supported the observations that azithromycin administration leaves the patient vulnerable to QTc interval prolongation and torsade de pointes.¹³

Basic electrophysiologic studies suggest that both drugs can provoke proarrhythmia via mechanisms beyond block of I_{Kr} implicated in usual cases of torsade de pointes.^{14,15} The effect of the combination of these agents on QT 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 risk of serious arrhythmias. These include hypokalemia, hypomagnesemia, fever,¹⁶ and an inflammatory state.¹⁷ Mechanisms to minimize arrhythmia risk include:

- Electrocardiographic/QT interval monitoring:
 - Withhold the drugs in patients with baseline QT prolongation (eg, QTc \geq 500 msec) or with known congenital long QT syndrome.
 - Monitor cardiac rhythm and QT interval; withdrawal of the drugs if QTc exceeds a preset threshold of 500 msec.
 - In patients critically ill with COVID-19 infection, frequent caregiver contact may need to be minimized, so optimal electrocardiographic interval and rhythm monitoring may not be possible.
- Correction of hypokalemia to levels of >4 mEq/L and hypomagnesemia to levels of >2 mg/dL.
- Avoid other QTc prolonging agents⁵ whenever feasible.



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

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

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Table. Torsade de pointes potential and post-marketing adverse events associated with possible COVID-19 repurposed pharmacotherapies.

Possible COVID-19 Treatment	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

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

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