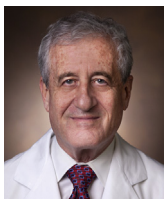
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.




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

References

1. Chen CY, Wang FL, Lin CC. Chronic hydroxychloroquine use associated with QT prolongation and refractory ventricular arrhythmia. Clin Toxicol (Phila) 2006;44:173–175.

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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

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

2. Morgan ND, Patel SV, Dvorkina O. Suspected hydroxychloroquine-associated QT-interval prolongation in a patient with systemic lupus erythematosus. J Clin Rheumatol 2013;19:286–288.
3. O'Laughlin JP, Mehta PH, Wong BC. Life threatening severe QTc prolongation in patient with systemic lupus erythematosus due to hydroxychloroquine. Case Reports in Cardiology 2016;2016:4626279.
4. de Olano J, Howland MA, Su MK, Hoffman RS, Biary R. Toxicokinetics of hydroxychloroquine following a massive overdose. Am J Emerg Med 2019;37. 2264.e5–e8.
5. Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc prolonging and torsadogenic potential of possible pharmacotherapies for COVID-19. Mayo Clin Proc. Available at: https://www.elsevier.com/__data/assets/pdf_file/0004/996745/MCP_Possible-COVID-19-Pharmacotherapies.pdf. Accessed April 2, 2020.
6. Choi Y, Lim H-S, Chung D, Choi J-G, Yoon D. Risk evaluation of azithromycin-induced QT prolongation in real-world practice. Biomed Res Int 2018;1574806.
7. Sears SP, Getz TW, Austin CO, Palmer WC, Boyd EA, Stancampiano FF. Incidence of sustained ventricular tachycardia in patients with prolonged QTc after the administration of azithromycin: a retrospective study. Drugs Real World Outcomes 2016;3:99–105.
8. Huang BH, Wu CH, Hsia CP, Yin Chen C. Azithromycin-induced torsade de pointes. Pacing Clin Electrophysiol 2007;30:1579–1582.
9. Kezerashvili A, Khattak H, Barsky A, Nazari R, Fisher JD. Azithromycin as a cause of QT-interval prolongation and torsade de pointes in the absence of other known precipitating factors. J Interv Card Electrophysiol 2007; 18:243–246.
10. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. N Engl J Med 2012;366:1881–1890.
11. Kim MH, Berkowitz C, Trohman RG. Polymorphic ventricular tachycardia with a normal QT interval following azithromycin. Pacing Clin Electrophysiol 2005; 28:1221–1222.
12. Yang Z, Prinsen JK, Bersell KR, et al. Azithromycin causes a novel proarrhythmic syndrome. Circ Arrhythm Electrophysiol 2017;10:e003560.
13. Mosholder AD, Mathew J, Alexander JJ, Smith H, Nambiar S. Cardiovascular risks with azithromycin and other antibacterial drugs. N Engl J Med 2013; 368:1665–1668.
14. Zhang M, Xie M, Li S, et al. Electrophysiologic studies on the risks and potential mechanism underlying the proarrhythmic nature of azithromycin. Cardiovasc Toxicol 2017;17:434–440.
15. Capel RA, Herring N, Kalla M, et al. Hydroxychloroquine reduces heart rate by modulating the hyperpolarization-activated current I_f: novel electrophysiological insights and therapeutic potential. Heart Rhythm 2015;12:2186–2194.
16. Kauthale RR, Dadarkar SS, Husain R, Karande VV, Gatne MM. Assessment of temperature-induced hERG channel blockade variation by drugs. J Appl Toxicol 2015;35:799–805.
17. Aromolaran AS, Srivastava U, Ali A, et al. Interleukin-6 inhibition of hERG underlies risk for acquired long QT in cardiac and systemic inflammation. PLoS ONE 2018;13:e0208321.
18. Simpson TF, Kovacs RJ, Stecker EC. Ventricular arrhythmia risk due to hydroxychloroquine-azithromycin treatment for COVID-19. Available at: https://www.acc.org/latest-in-cardiology/articles/2020/03/27/14/00/ventricular-arrhythmia-risk-due-to-hydroxychloroquine-azithromycin-treatment-for-covid-19. Accessed April 2, 2020.