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RESEARCH LETTER

Association of Hydroxychloroquine With QTc Interval in Patients With COVID-19

Andrea Mazzanti, MD, PhD
Silvia G. Priori, MD, PhD

Hydroxychloroquine is currently prescribed in many countries as a treatment for patients with coronavirus disease 2019 (COVID-19). The notion that hydroxychloroquine blocks the hERG (human ether-a-go-go-related gene) potassium channel, potentially leading to QT interval prolongation and arrhythmias, mitigates the enthusiasm for the compound. Recent studies conducted on cohorts of COVID-19 patients treated with hydroxychloroquine reported different signals, ranging from serious concern related to 20% of patients with major corrected QT (QTc) interval prolongation,[1] to more reassuring data.[2]

The potential benefit of hydroxychloroquine underscores the need to evaluate the QTc prolongation during the short-term treatment with hydroxychloroquine used in COVID-19. In particular, the effect of combining hydroxychloroquine with other hERG-blocking drugs such as azithromycin, or lopinavir/ritonavir should be assessed.

An ongoing, observational, prospective study was established to determine whether the short-term use of hydroxychloroquine alone, or in combination with at least 1 other hERG-blocking COVID-19 drug, is associated with an excessive QT prolongation, defined as QTc interval ≥500 ms. The study protocol was approved by the ethics committees of the participating centers, and patients provided informed consent.

Between March 7, 2020, and April 30, 2020, we enrolled 150 consecutive inpatients (63% men; median age 69 years, interquartile range [IQR] 57–81 years; 46% with hypertension and 19% with diabetes mellitus) with a diagnosis of COVID-19 confirmed by polymerase chain reaction, who were admitted to our hospitals and were treated with hydroxychloroquine for a median of 9 days (IQR 5–11 days), at a daily dosage of 400 mg (97%), or 600 mg (3%). In 67% of cases, hydroxychloroquine was associated with azithromycin (26%), lopinavir/ritonavir (35%), or azithromycin+lopinavir/ritonavir (6%).

A 12-lead ECG was recorded after a median of 5 days (IQR 3–7 days) of treatment. The QT interval was corrected using the Bazett formula. In patients with atrial fibrillation (7%), the QTc interval was calculated as an averaged value over 3 consecutive cycles. In patients with significant intraventricular conduction delays (ie, QRS >120 ms), which were observed in 14% of cases, we applied the formula for QT adjustment proposed by Rautaharju.[3]

The median QTc interval on treatment with hydroxychloroquine was 433 ms (IQR 414–447 ms), without differences between hydroxychloroquine monotherapy and combination therapies with azithromycin, lopinavir/ritonavir, or azithromycin+lopinavir/ritonavir (P=0.742; Kruskal-Wallis test). Overall, the proportion of patients with mild (460–479 ms), intermediate (480–499 ms), and severe (≥500 ms) QTc prolongation was 9%, 4%, and 2%, respectively. Since some patients had an ECG recorded before the termination of therapy, we cannot

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exclude that we might have missed the maximal effect of the drug on QTc interval. Nonetheless, the QTc interval did not differ significantly based on the time of ECG recording. As expected over a short follow-up on therapy, no life-threatening arrhythmic events were documented.

In 79 of the 150 patients (53%) with an ECG off-therapy also available (Figure), the median QTc interval was 414 ms (IQR 397–436 ms) at baseline and 435 ms (IQR 416–451 ms) during treatment, with a median increase of 18 ms (IQR 2–34 ms; *P*<0.001; Wilcoxon signed-rank test), similarly to that observed by Saleh.[2] The heart rate did not change, being 75 bpm (IQR 74–85 bpm) at baseline and 75 bpm during treatment (IQR 77–82 bpm; *P*=0.690). The PR interval prolonged by a median of 6 ms (IQR –5 to 20 ms), from 163 ms (IQR 150–180 ms) to 165 ms (IQR 153–186 ms; *P*=0.006), and 4 patients developed a new first-degree atrioventricular block. The QRS interval lengthened by a median of 4 ms (IQR –1 to 8 ms), from 92 ms (IQR 85–102 ms) to 96 ms (IQR 88–105 ms; *P*=0.053).

The robust method used permitted us to correctly evaluate the QT interval, even in patients with intraventricular conduction delays. Our findings are relevant, given that most patients (85%) were treated with at least 1 QT-prolonging drug other than hydroxychloroquine. Still, most subjects (84%) had a QTc not exceeding 460 ms.

Whereas the last word on the safety of hydroxychloroquine in the treatment of COVID-19 will come from the ongoing randomized studies, our data suggest that a cumulative hydroxychloroquine dose of 2 g over 5 days, as adopted in 30% of all ongoing hydroxychloroquine trials (www.clinicaltrials.gov) leads to a modest prolongation of QTc in patients with a normal baseline QTc. It is remarkable that 85% of our patients also received another QT-prolonging treatment beside hydroxychloroquine.

We believe that because hydroxychloroquine reaches the steady state after 180 days on therapy,[4] the

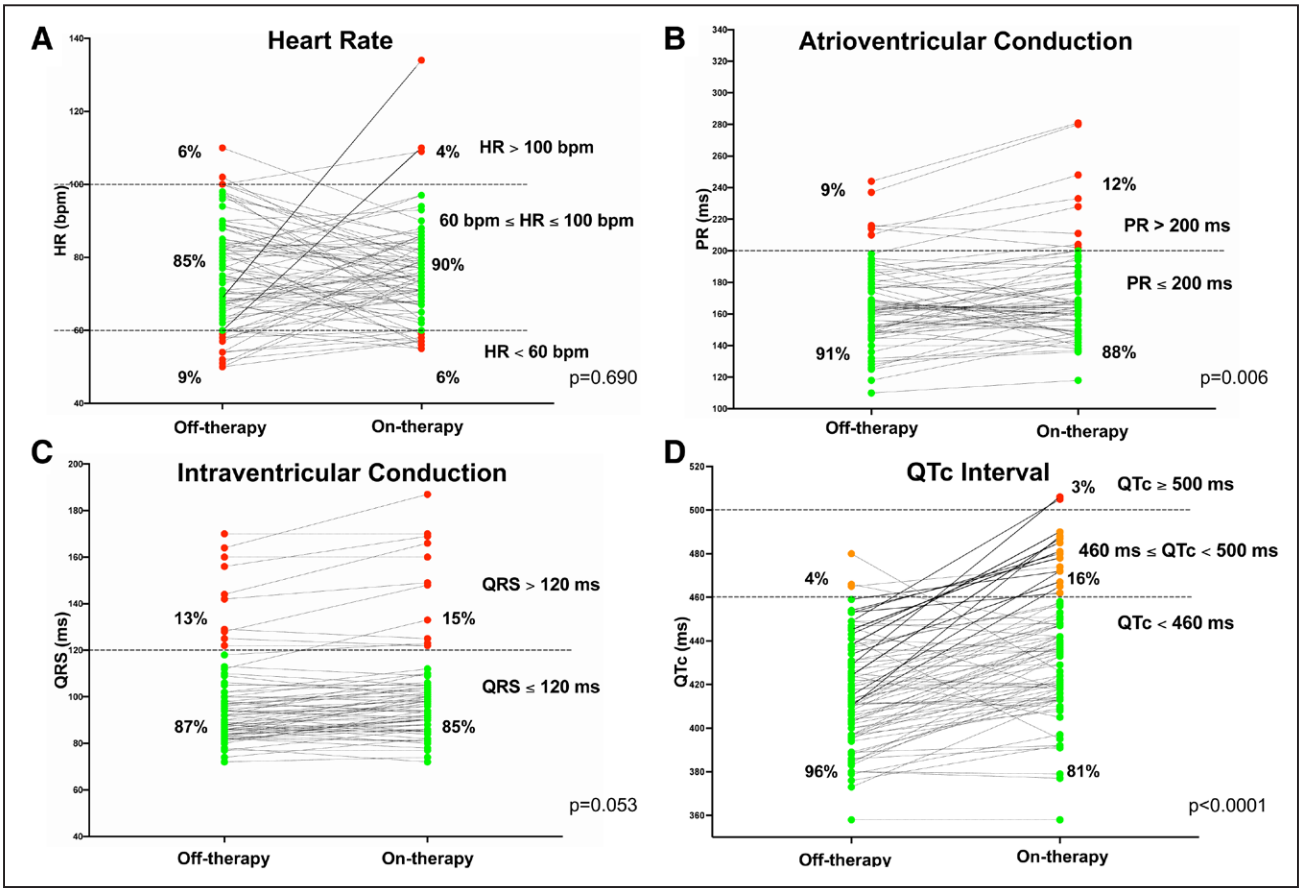

Figure. Effect of hydroxychloroquine on ECG interval values.
Comparison of ECG interval values for 79/150 (53%) patients for whom an ECG off-therapy and an ECG during hydroxychloroquine treatment was available. Each line represents the ECG parameters (heart rate, PR interval, QRS interval, and QTc interval) off-therapy and during hydroxychloroquine treatment. Circles are color-coded: green, if the values are normal; orange, if the values are intermediately abnormal; red, if severely abnormal. **A**, The heart rate during treatment did not change (median change 1 bpm, interquartile range [IQR] –11 to 9 bpm), from 75 bpm (IQR 74–85 bpm) at baseline to 75 bpm during treatment (IQR 77–82 bpm; *P*=0.690, Wilcoxon signed-rank test). **B**, The PR interval prolonged by a median of 6 ms (IQR –5 to 20 ms), from 163 ms (IQR 150–180 ms) to 165 ms (IQR 153–186 ms; *P*=0.006; Wilcoxon signed-rank test). During hydroxychloroquine therapy, 4 patients developed a new first-degree atrioventricular block. **C**, The QRS interval lengthened by a median of 4 ms (IQR –1 to 8 ms), from 92 ms (IQR 85–102 ms) to 96 ms (IQR 88–105 ms; *P*=0.053, Wilcoxon signed-rank test). **D**, The QTc interval increased by a median of 18 ms (IQR 2–34 ms) from 414 ms (IQR 397–436 ms) to 435 (IQR 416–451 ms; *P*<0.001, Wilcoxon signed-rank test). HR indicates heart rate; and QTC, corrected QT.

observed modest effect on QTc prolongation is because of the short duration of treatment adopted in COVID-19. It is expected that safety data on patients treated for several years for other indications could show a more severe QTc prolongation. Meanwhile, a baseline ECG should be performed before starting hydroxychloroquine, followed by a subsequent recording on therapy for patients with a normal baseline QTc. Daily monitoring is advisable for patients with baseline QTc >480 ms.

ARTICLE INFORMATION

Data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors

Andrea Mazzanti, MD, PhD; Martina Briani, MD; Deni Kukavica, MD; Francesca Bulian, MD; Stefano Marelli, MD; Alessandro Trancuccio, MD; Nicola Monteforte, MD; Tommaso Manciulli, MD, PhD; Massimo Morini, DEng; Annalisa Carlucci, MD; Giacomo Viggiani, BSc; Francesco Cannata, MD; Sara Negri, MSc; Raffaella Bloise, MD; Mirella Memmi, BSc; Patrick Gambelli, BSc; Andrea Carbone, MD; Martina Molteni, MD; Raffaella Bianchini, RN; Rita Salgarello, RN; Silvia Sozzi, RN; Pasquale De Cata, MD; Francesco Fanfulla, MD; Piero Ceriana, MD; Carlo Locatelli, MD; Carlo Napolitano, MD, PhD; Luca Chiovato, MD, PhD; Luca Tomasi, MD; Giulio G. Stefanini, MD, PhD; Gianluigi Condorelli, MD, PhD; Silvia G. Priori, MD, PhD

Correspondence

Silvia G. Priori, MD, PhD, Molecular Cardiology – IRCCS ICS Maugeri, Via Maugeri, 10 - 27100 Pavia, Italy. Email silvia.priori@icsmaugeri.it

Affiliations

IRCCS Istituti Clinici Scientifici Maugeri, Pavia, Italy (A.M., D.K., S.M., A.T., N.M., T.M., M.Morini, A.C., S.N., R.B., M.Memmi, P.G., A.C., M.Molteni, R.B., R.S., S.S., P.D.C., F.F., P.C., C.L., C.N., L.C., S.G.P.). Department of Molecular Medicine (A.M, D.K., C.N., S.G.P.), Department of Internal Medicine (L.C.), University of Pavia, Italy. ERN Guard-Heart European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart (A.M., C.N., S.G.P.). Humanitas Clinical and Research Center – IRCCS, Rozzano (MI), Italy (M.B., F.C., G.G.S., G.C.). Azienda Ospedaliera Universitaria Integrata Verona, Italy (F.B., L.T.). University of Pavia, Italy (T.M.). Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy (G.V., F.C., G.G.S., G.C.). Molecular Cardiology, Fundación Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain (S.G.P.).

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Disclosures

None.

REFERENCES

1. Mercuro NJ, Yen CF, Shim DJ, Maher TR, McCoy CM, Zimetbaum PJ, Gold HS. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19) [published online May 1, 2020]. *JAMA Cardiol*. doi: 10.1001/jamacardio.2020.1834. https://jamanetwork.com/journals/jamacardiology/fullarticle/2765631
2. Saleh M, Gabriels J, Chang D, Kim BS, Mansoor A, Mahmood E, Makker P, Ismail H, Goldner B, Willner J, et al. Effect of chloroquine, hydroxychloroquine, and azithromycin on the corrected QT interval in patients with SARS-CoV-2 infection. *Circ Arrhythmia Electrophysiol*. 2020;13:e008662. doi: 10.1161/CIRCEP.120.008662
3. Rautaharju PM, Surawicz B, Gettes LS, Bailey JJ, Childers R, Deal BJ, Gorgels A, Hancock EW, Josephson M, Kligfield P, et al; American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; American College of Cardiology Foundation; Heart Rhythm Society. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. *Circulation*. 2009;119:e241–e250. doi: 10.1161/CIRCULATIONAHA.108.191096
4. Carmichael SJ, Charles B, Tett SE. Population pharmacokinetics of hydroxychloroquine in patients with rheumatoid arthritis. *Ther Drug Monit*. 2003;25:671–681. doi: 10.1097/00007691-200312000-00005