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Acute QT Interval Modifications During Hydroxychloroquine-Azithromycin Treatment in the Context of COVID-19 Infection

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Abstract

Among candidate drugs to treat coronavirus disease 2019 (COVID-19), the combination of hydroxychloroquine (HCQ) and azithromycin (AZ) has received intense worldwide attention. Even as the efficacy of this combination is under evaluation, clinicians have begun to use it largely. As these medications are known to prolong the QT interval, we analyzed serial electrocardiograms recorded in patients hospitalized for COVID-19 pneumonia and treated with HCQ + AZ. Fifty consecutive patients received the combination of HCQ (600 mg/d for 10 days) and AZ (500 mg/d on day 1 and 250 mg/d from day 2 to day 5). Twelve-lead electrocardiograms were recorded before treatment, at day 3, at day 5, and at discharge. The median age of patients was 68 years (interquartile range, 53-81 years); 28 (56%) were men. The main comorbidities were hypertension (36%; n=18) and diabetes (16%; n=8). The mean corrected QT (QTc) interval was 408 ms at baseline and increased up to 437 ms at day 3 and to 456 ms at day 5. Thirty-eight patients (76%) presented short-term modifications of the QTc duration (>30 ms). Treatment discontinuation was decided in 6 patients (12%), leading to QTc normalization in 5 of them. No deaths and no cardiac arrhythmic events were observed in this cohort. Our report confirms that a short duration treatment with HCQ + AZ modifies the QTc interval. The treatment had to be discontinued for QTc modifications in 12% of patients. Nevertheless, in inpatients hospitalized for COVID-19, we did not observe any clinically relevant consequences of these transitory modifications. In conclusion, when patients are treated with HCQ + AZ, cardiac monitoring should be regularly performed and hospital settings allow monitoring under in safe conditions.

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Since December 2019, the world has faced an emerging and pandemic of coronavirus disease 2019 (COVID-19), leading to severe acute respiratory syndrome caused by a newly discovered coronavirus, severe acute respiratory syndrome coronavirus 2. At the time of the submission of this report (mid-April 2020), 2 million people were already infected across the world, resulting in 150,000 deaths.¹ Thus, there is an urgent need for both effective and safe treatments to prevent hypoxemic respiratory failure and death.² Among candidate drugs to treat COVID-19, hydroxychloroquine (HCQ) and

azithromycin (AZ) have received intense worldwide attention. Hydroxychloroquine was recently associated with viral load reduction both in vitro and in infected patients, alone or combined with AZ.^{3,4} Even as the clinical efficacy of HCQ +/- AZ is still under evaluation with controversial results, these agents, alone or combined, are up to now among the most largely tested and clinicians have begun to use them for compassionate reasons in patients with COVID-19.^{5,6} In early April 2020, the Food and Drug Administration issued an Emergency Use Authorization for HCQ in the treatment of patients with COVID-19.⁷

However, as HCQ and AZ are medications known to prolong the QT interval, their large use raises concerns about the potential risk of “torsades de pointes” (TdP) and arrhythmic death.⁸ This warning was recently pointed out by several scientific societies and national health authorities, which reinforce that such treatments given in the context of COVID-19 should be exclusively monitored at the hospital level, notably in the elderly population with frequent concomitant cardiac disease or electrolyte disorders (ie, hypokalemia, hypomagnesemia, and hypocalcemia).⁹⁻¹² The effect of HCQ on ventricular repolarization is known to be dose dependent but considerable varies among individuals.¹³⁻¹⁵ Azithromycin does not usually cause a marked prolongation of the corrected QT (QTc) interval, but its use in combination with HCQ could theoretically increase the risk of TdP.¹⁶ To date, there are limited data evaluating the electrocardiographic (ECG) modifications induced by the combination therapy¹⁷ and very few in the context of COVID-19 infection.^{18,19}

Given the vast adoption of this regimen, we decided to analyze serial ECGs recorded in patients hospitalized in our department for COVID-19 pneumonia and treated with both HCQ and AZ.

PATIENTS AND METHODS

From March 18, 2020, through March 25, 2020, 50 consecutive patients were proposed to be treated with the combination of HCQ (600 mg/d for 10 days) and AZ (500 mg/d on day 1 and 250 mg/d from day 2 to day 5). Twelve-lead ECGs were recorded in each patient before treatment, 3 and 5 days after treatment, and on the day of discharge. The treatment was not initiated in patients with contraindications, including hypokalemia, or when the QTc interval was more than 500 ms, taking as a reference the Bazett formula. The treatment was discontinued if there was a QTc increase of 60 ms compared with baseline or when the QTc interval was more than 500 ms.²⁰ We also paid close attention to potential drug interactions, especially those that could prolong the QTc interval (ie,

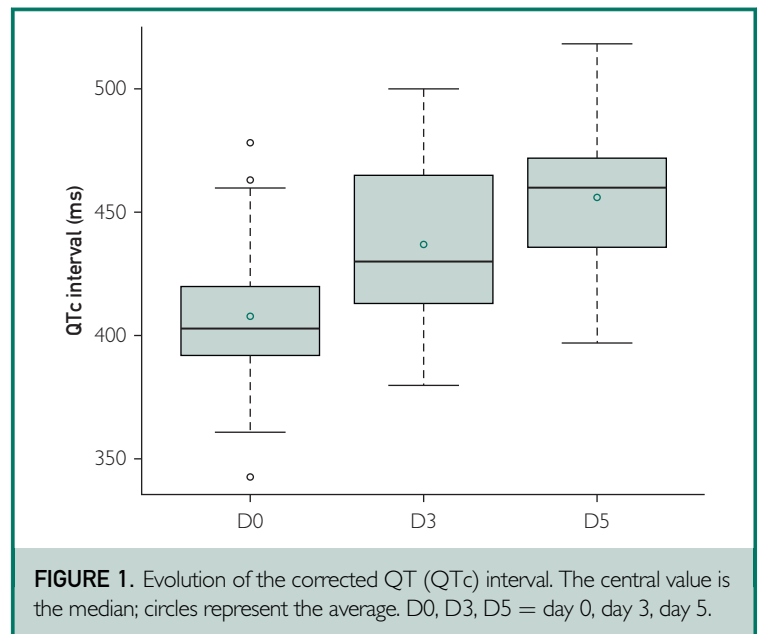
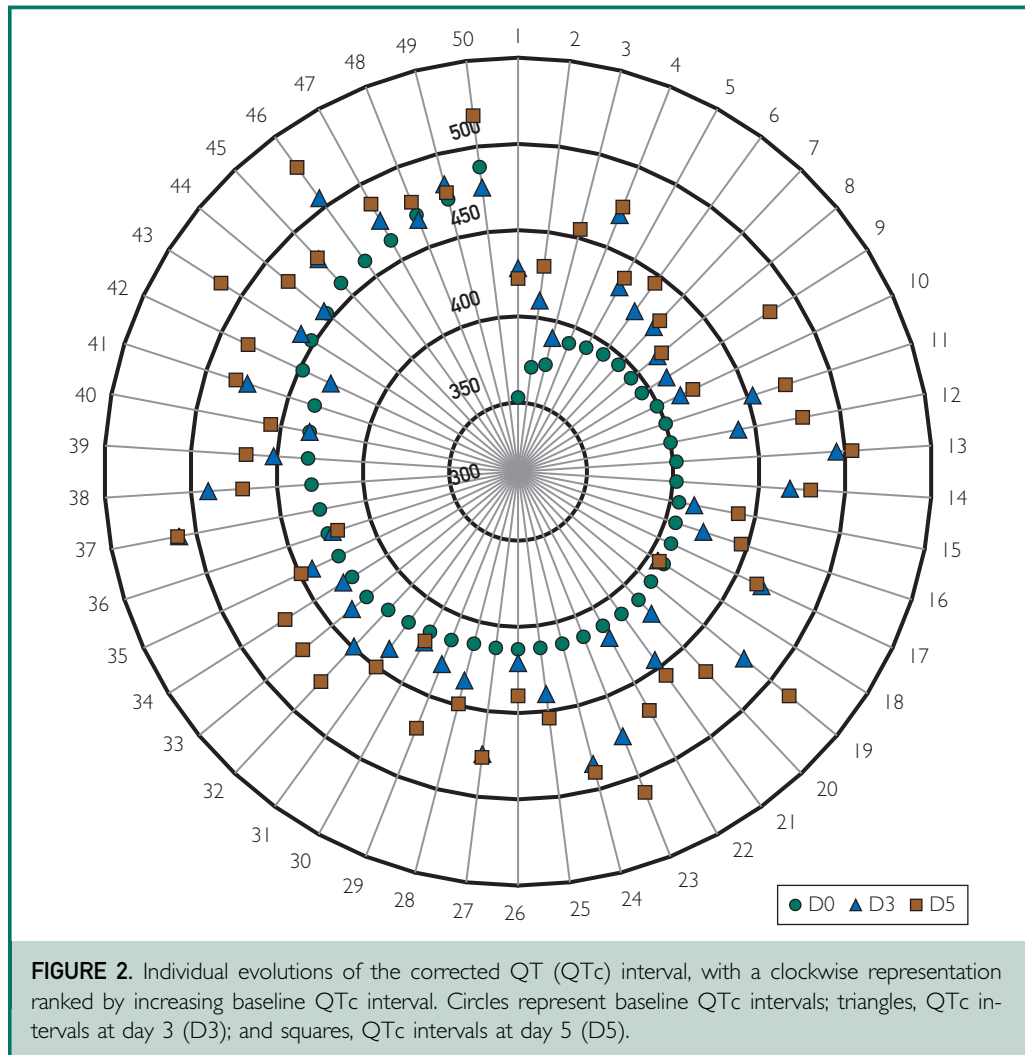


FIGURE 1. Evolution of the corrected QT (QTc) interval. The central value is the median; circles represent the average. D0, D3, D5 = day 0, day 3, day 5.

antiarrhythmics: disopyramide, procainamide, quinidine, and sotalol; *antidepressants:* citalopram, escitalopram; *antiemetics:* dolasetron, droperidol, granisetron, and ondansetron; *antifungals:* fluconazole, ketoconazole, pentamidine, and voriconazole; *antipsychotics:* haloperidol, thioridazine, and ziprasidone; *fluoroquinolones:* ciprofloxacin, levofloxacin, and moxifloxacin; *macrolides:* azithromycin, clarithromycin, and erythromycin; *opioids:* methadone; *miscellaneous:* cocaine, cilostazol, and donepezil).^{20,21}

RESULTS

The median age of patients was 68 years (interquartile range [IQR], 53-81 years); 55.2% of patients were men. A history of cardiovascular disease was reported in 44% of patients; the prevalence of treated hypertension and diabetes was 36% and 16%, respectively. The median interval time between symptom onset and hospital admission was 8 days (IQR, 5-10 days), with a majority (52%) of patients admitted after 5 days of symptom onset. A pulmonary computed tomography scan was available in 95% of patients. Fifty-four percent of patients presented upon admission an extended to critical form of pulmonary lesions. The mean QTc interval was 408 ms (IQR,



343-478 ms) at baseline and increased up to 437 ms (IQR, 380-500 ms) at day 3 and to 456 ms (IQR, 397-518 ms) at day 5. The median QTc interval at day 0, day 3, and day 5 was 403, 430, and 460 ms, respectively (Figure 1). We could record an ECG on the day of discharge in 20 of these patients for whom treatment had been completed for at least 3 days. For these patients, the QTc interval at day 5 was 460 ms (IQR, 397-518 ms) and decreased to 427 ms at discharge (IQR, 390-500 ms). Individual evolutions of the QTc interval are depicted in Figure 2, with a clockwise representation ranked by increasing baseline QTc interval. Thirty-eight patients (76 %) presented short-term modifications of the QTc duration (ie, >30

ms). Premature discontinuation of the combination due to prespecified QTc criteria was decided in 6 patients (12%). Of these 6 patients, 5 normalized their QTc values when treatment was discontinued. One patient remained stable (500 ms) at day 2 after withdrawal and then was discharged. In the population in which HCQ + AZ had to be interrupted, the mean baseline QTc interval was higher than that in the global population of this study (433 and 408 ms, respectively). No death, no clinical cardiac event, nor TdP was observed in this cohort.

DISCUSSION

These results indicate that the treatment with HCQ + AZ significantly and progressively

increases QTc intervals (29 ms at day 3 and 48 ms at day 5). These increases appear to be dose and time dependent, as previously described in the literature.¹⁶ Importantly, QTc intervals decrease when AZ was discontinued and HCQ maintained between day 5 and discharge. They confirm the need for regular cardiac monitoring even if the treatment had to be discontinued in a relatively small proportion of patients (12%). Hospital settings seem to be an appropriate location to perform the monitoring according to the number of ECGs needed. Interestingly, higher baseline QTc intervals were observed in the population in which HCQ + AZ has to be interrupted, highlighting the need for careful monitoring when the initial QTc values are above 430 ms.

To date, there are very few data evaluating the ECG modifications induced by the HCQ + AZ combination in the context of COVID-19 infection. In a retrospective study of 84 patients, Chorin et al¹⁹ reported that in 30% of patients the QTc interval increased by more than 40 ms. In 11% of patients, the QTc interval increased to more than 500 ms. These findings are in line with our results. Interestingly, the authors noted that the development of acute renal failure but not the baseline QTc interval was a strong predictor of extreme QTc prolongation.¹⁹ More recently, Mahevas et al⁶ performed a cohort study with 84 patients with severe acute respiratory syndrome coronavirus 2 pneumonia treated with HCQ. Even if the proportion of patients concomitantly receiving HCQ + AZ was not described in the study, 9.5% of patients experienced ECG modifications requiring HCQ discontinuation at a median of 4 days after its introduction. Here again, these results are in line with our findings, highlighting the additive effect, even if probably moderate, of AZ on QT modification when combined to HCQ.

Our study has several limitations. First, its monocentric character with a limited number of patients is the most important. Second, ECG monitoring data were not available after discharge. Finally, it is still premature to consider HCQ + AZ as a validated

option to treat patients with COVID-19. However, our study allows a preliminary assessment of the electrophysiological safety of a treatment that is currently largely used in the context of COVID-19 infection.

CONCLUSION

These results confirmed that a short duration treatment with the combination of HCQ and AZ does modify the QTc interval. Nevertheless, in inpatients hospitalized for COVID-19, we did not observe any clinically relevant consequence of these transitory modifications. The treatment had to be discontinued for QTc modifications in 12% of patients. In conclusion, when patients are treated with the combination of HCQ and AZ, cardiac monitoring should be regularly performed and hospital settings allow monitoring under in safe conditions.

Abbreviations and Acronyms: AZ = azithromycin; COVID-19 = coronavirus disease 2019; ECG = electrocardiogram; HCQ = hydroxychloroquine; IQR = interquartile range; TdP = torsades de pointes

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