Incidence of QTc interval prolongation in patients treated for covid-19 with Doubase C or Hydroxychloroquine-azithromycin at University Hospital of Kinshasa

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Abstract

**Background:** QTc prolongation has been described in COVID-19 patients treated with Hydroxychloroquine (HCQ) and Azithromycin (AZT) in western countries. In the Democratic Republic of the Congo (DRC), few studies have assessed the safety of these molecules, and neither have they for new molecules proposed for COVID-19 treatment, such as Doubase C. This study aimed to determine the incidence of QTc prolongation in COVID-19 patients treated with HCQ-AZT or Doubase C.

**Methods:** This study was part of a randomized clinical trial. Data were collected from May 20, 2021, to January 15, 2022. Patients were randomized into two arms; one was treated with Doubase C and the other with HCQ-AZT at standard dosages. Only patients with mild to moderate COVID-19 were included.

**Results:** A total of 261 patients were included. At inclusion, the two groups were comparable (52.5% men, 47.5% women, mean age 41±15 years. The incidence of prolonged QTc interval was 1.5% in the whole group (3.3% on the HCQ-AZT arm and 0% on the Doubase C arm). No ventricular arrhythmias or torsade de pointes, or cardiac arrest were observed.

**Conclusion:** Unlike Doubase C, the HCQ-AZT strategy has a risk of QTc prolongation.

Introduction

The first cases of coronavirus disease 2019 (COVID-19) were reported in December 2019 in people presenting pneumonia in Wuhan, China (1). After that, COVID-19 rapidly spread outside China and was declared a pandemic by the World Health Organization (WHO) on March 11th, 2020 (2). Its curative treatment is fraught with controversy. Some studies in patients with mild to moderate clinical presentations have suggested the benefits of hydroxychloroquine (HCQ) alone or in combination with azithromycin (AZT). The most reported adverse effects of HCQ are allergy and retinal damage. There is little evidence of HCQ and AZT’s effect on COVID-19 mortality reduction. In contrast, these molecules are likely to increase the risk of cardiac arrhythmia by prolonging the QTc interval (3–5). Several studies have shown that HCQ and chloroquine (CQ) prolong the QTc interval in humans in a dose- and concentration-dependent manner (6, 7). In a systematic review, Lior Jankelson et al. found that approximately 10% of COVID-19 patients treated with HCQ or CQ developed QTc prolongation (8). This risk is increased when AZT is added to the treatment. This prolongation of the QTc interval is likely to evolve potentially into torsade de pointes and thus increase the patient’s mortality. In France, Francis Bessière et al. found that QT intervals increased in more than 90% of patients, raising concerns about the widespread use of HCQ with or without AZT (9). Therefore, QTc intervals should be monitored by recording a baseline electrocardiogram and then another electrocardiogram during CQ or HCQ treatment course (10). Complications following CQ or HCQ treatment have limited their use in Europe to manage COVID-19 (11).

In the US, guidelines suggest that HCQ and CQ should be administered in hospitalized COVID-19 patients with evidence of pneumonia. However, no solid clinical trials have shown the efficacy of these molecules (10).
In the DRC and several African countries, HCQ, in combination with AZT, was chosen as the first choice of COVID-19 treatment based on previous experience in using HCQ, mainly for treating malaria. Reports on the cardiac toxicity of HCQ in Africa are scarce, especially in the management of malaria and rheumatological diseases. To address complications related to the use of HCQ and AZT for COVID-19 treatment, the DRC ministry of research has encouraged clinical trials on alternative molecules. Doubase C is one of the molecules approved for clinical trials on COVID-19 patients (Ministry of Scientific Research, number: 444/MIN.RSIT/CABMIN/JMK/2020). It is a molecule from phytotherapy produced by the CREPPAT research laboratory. The molecule obtained its marketing authorization in 2017 (MA: MS.1253/10/05/DEM/0314/2017 Ministry of Health/DRC). It was initially approved for the treatment of HIV infection. It is produced from extracts of Uvaria sp (30 mg) and Harungana sp (6 mg). Its action on the envelope of the virus and lysosomes gives it a broad-spectrum antiviral activity.

The present study was conducted to evaluate the extent of cardiac complications (QTc prolongation) in patients included in the Doubase C versus HCQ-AZT clinical trial at CUK, as the cardiac safety of these two therapeutic strategies has never been evaluated.

**Methods**

**Study design, setting, and period**

This study was part of a randomized clinical trial that evaluated the efficacy and safety of two therapeutic strategies used in the DRC to treat COVID-19: HCQ-AZT and Doubase C.

We mainly focused on assessing the cardiac safety of these two therapeutic strategies. We collected data from the COVID-19 Treatment Center (CTCO) of the University Hospital of Kinshasa (French acronym CUK) from May 20, 2021, to January 15, 2022, corresponding to the 3rd and 4th waves of the COVID-19 epidemic in DRC.

**Sampling**

We included patients enrolled in the clinical trial who performed an electrocardiogram before and after treatment. Electrocardiograms were performed on day 1 and day 14. Pregnant women and patients with prolonged QTc interval on day one or heart failure were excluded.

We also excluded patients with serum creatinine greater than 110 µmol/L, Glomerular Filtration Rate < 60 ml/min/1.73 m², AST and ALT > 40 IU/L, Total bilirubin > 2 mg/dL) or a known allergy to any drugs used in the clinical trial.

**Patient randomization and intervention**

Patients were allocated into two arms using a randomization table.

The first arm consisted of patients who were treated using Doubase C according to the scheme below:
< 80 kg: 3x2 tablets/day for 7 days to be chewed with meals

80–100 kg: 3x3 tablets/day for seven days to be chewed with meals

> 100 Kg: 3x4 tablets/day for seven days to be chewed with meals

The second arm consisted of patients treated according to the national protocol scheme using HCQ-AZT:

HCQ: 3x200 mg/day for 10 days

AZT: 500 mg the first day, then 250 mg daily from the 2nd to the 5th.

**Samples collection and analysis**

Samples were collected for fasting blood tests and analyzed at the CUK CTCO laboratory.

Hemoglobin rates were determined using Mindray BC-20 S automated system. Creatinine, AST, and ALT assays were performed on Mindray BC-240. Blood gas and ions were tested using the EDAN i 15 automated system.

**Electrocardiogram**

Twelve-lead ECGs were recorded at 25 mm/s using a MAC ECG 600 machine on day 1 and day 14 of randomization. Two cardiologists blindly interpreted electrocardiograms, and consensus results were considered.

PR, QRS, QT, and QTc intervals were measured automatically by the device and checked manually. The lead showing the longest QTc interval was used to calculate the QTc interval. This was either D2 or V5 (11). The Bazett formula was used to calculate the QTc interval when the heart rate was between 60 and 100 beats per minute (11), and the Fridericia formula when the heart rate was less than 60 beats per minute or greater than 100 beats per minute.

For patients with intraventricular conduction delays (bundle branch block), a modified QTc was calculated using the JTC formula: (QT- (QRS-120 milliseconds))/√RR (11).

**Operational Definitions**

- SARS-CoV-2 infection was defined as a positive reverse transcriptase-polymerase chain reaction (RT-PCR) test result on nasopharyngeal or oropharyngeal swab samples (13).
- Asymptomatic COVID-19 was defined in patients without clinical symptoms and oxygen saturation of at least 95% (13).
- Mild COVID-19 was defined in any COVID-19 patient with few or no symptoms, temperature < 38.5°C, normal respiratory rate (between 12 and 20 breaths per minute), and oxygen saturation ≥ 95% (13).
- Any COVID-19 patient with a temperature ≥ 38.5°C, a respiratory rate between 20 and 30 breaths per minute, and blood oxygen saturation between 90 and 94% were considered moderate COVID-19 (13).
• A patient with clinical signs of pneumonia (fever, cough, dyspnea, rapid breathing) plus the following signs or symptoms: respiratory rate greater than 30/minute; severe respiratory distress; or SpO2 less than 90% on room air was considered to have severe COVID-19 (13).

• Critical COVID-19 was defined as acute respiratory distress syndrome, organ failure requiring ventilatory support or dialysis (13).

• QT interval was defined as the duration from the beginning of the QRS complex to the end of the T wave on its return to baseline, ideally measured using lead D2 or lead V5 of the 12-lead ECG.

• Prolonged QTc interval was defined as a QTc interval greater than 450 msec for men and greater than 470 ms for women (14).

• QTc interval requiring discontinuation was defined by a prolonged QTc interval ≥ 500 ms (15) and by a QTc increase of > 80 ms (Δ ≥ 80 msec).

**Statistical Analyses.**

Data were entered using Excel software, and analyses were performed using IBM SPSS Statistics version 25.0. Categorical variables were presented as absolute and relative frequency (%). Continuous variables were presented as means ± standard deviation.

The Kolmogorov-Smirnov test assessed the normal distribution of each variable.

The student t-test was used to compare the means of the two groups. The Mac Nemar test was used to compare paired data. The threshold for statistical significance was set at 0.05

**Ethics approval**

Data were collected anonymously and confidentially concerning patients’ privacy. We ensured that the three fundamental principles of ethics were respected during the study: the principle of respect for the individual, beneficence, and justice to the Declaration of Helsinki. Patients were provided free healthcare. The University of Kinshasa Faculty of Medicine pharmacovigilance team developed the therapeutic protocol according to the WHO standard protocol (version 1.0 of June 09, 2020).

We obtained a favorable opinion from the pharmaceutical research laboratory, CREPPAT, to conduct the present study. This study was part of the Doublease C versus HCQ-AZT clinical trial, which was approved by the Ethics committee of the Kinshasa School of Public Health (ESP/CE/038/2021).

**Results**

We included a total of 261 patients who were randomly allocated into two arms: 123 (47%) were treated with HCQ-AZT, and 138 (53%) with Doublease C.

The mean age of the patients was 41 ±15 years with a sex ratio of 1.1. Male participants were more represented in the HCQ-AZT arm (52.5%) and female participants (53.6%) in the Doublease C arm (Table 1). The mean BMI of the patients was 26 ± 5 Kg/m², and the mean partial oxygen saturation was 97 ± 2%.
Ninety-three percent of the patients had mild COVID-19 disease. Patients with medical history of hypertension, diabetes, HIV/AIDS, asthma, and tuberculosis represented 14%, 4%, 3%, 0.5%, and 0.5% respectively. The mean hemoglobin was 14 ± 3 g/dl, the mean creatinine 0.97 ± 0.3 mg/dl, and the mean AST and ALT were 28 ± 12 and 25 ± 16 IU/l, respectively. There was no statistical difference in the distribution of patients in the two arms (Table 1).

Table 1. Participant's general characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Participants</th>
<th>Doubase C</th>
<th>HCQ-AZT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antecedents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>29(14)</td>
<td>18(15)</td>
<td>11(12)</td>
<td>0.359</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9(4)</td>
<td>7(6)</td>
<td>2(2)</td>
<td>0.173</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1(0.5)</td>
<td>1(0.8)</td>
<td>0</td>
<td>0.572</td>
</tr>
<tr>
<td>Asthma</td>
<td>6(3)</td>
<td>3(3)</td>
<td>3(3)</td>
<td>0.528</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1(0,5)</td>
<td>1(0,8)</td>
<td>0</td>
<td>0.569</td>
</tr>
<tr>
<td>Biology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>14 ± 3</td>
<td>14 ± 3</td>
<td>14 ± 2</td>
<td>0.673</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.97 ± 0,3</td>
<td>0.96 ± 0,3</td>
<td>0.99 ± 0,25</td>
<td>0.420</td>
</tr>
<tr>
<td>ALAT (UI/L)</td>
<td>25 ± 16</td>
<td>23 ± 14</td>
<td>27 ± 18</td>
<td>0.064</td>
</tr>
<tr>
<td>ASAT (UI/L)</td>
<td>28 ±12</td>
<td>29 ± 14</td>
<td>26 ± 11</td>
<td>0.141</td>
</tr>
<tr>
<td>K⁺(mmol/l)</td>
<td>4,2 ± 2</td>
<td>3,9 ± 1,0</td>
<td>3,8 ± 0,11</td>
<td>0,167</td>
</tr>
<tr>
<td>Ca ²⁺ (méq/l)</td>
<td>1,17 ± 0,11</td>
<td>1,15 ± 0,11</td>
<td>1,18 ± 0,11</td>
<td>0,430</td>
</tr>
</tbody>
</table>

All patients had sinus rhythm, with a mean heart rate of 78 ± 13 per minute, a mean PR space at 170 ± 28 ms, a mean QRS at 76±13 ms, and a mean QTc at 405 ± 30 ms (Table 2).

Table 2. EKG characteristics of patients before initiation of treatment
### EKG parameters

<table>
<thead>
<tr>
<th>EKG parameters</th>
<th>Participants</th>
<th>Doubase C</th>
<th>HCQ-AZT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus rythm</td>
<td>261(100)</td>
<td>123(100)</td>
<td>138(100)</td>
<td>.</td>
</tr>
<tr>
<td>Heart rate (per minute)</td>
<td>78 ± 13</td>
<td>79 ± 13</td>
<td>77 ± 13</td>
<td>0,420</td>
</tr>
<tr>
<td>P wave (ms)</td>
<td>114 ± 10</td>
<td>113 ± 12</td>
<td>115 ± 8</td>
<td>0,495</td>
</tr>
<tr>
<td>PR space (ms)</td>
<td>170 ± 28</td>
<td>172 ± 30</td>
<td>168 ± 26</td>
<td>0,331</td>
</tr>
<tr>
<td>QRS complex (ms)</td>
<td>76 ± 13</td>
<td>76 ± 14</td>
<td>76 ± 12</td>
<td>0,839</td>
</tr>
<tr>
<td>T wave (ms)</td>
<td>193 ± 32</td>
<td>193 ± 30</td>
<td>194 ± 34</td>
<td>0,679</td>
</tr>
<tr>
<td>QTc interval (ms)</td>
<td>405 ± 30</td>
<td>406 ± 31</td>
<td>401 ± 29</td>
<td>0,193</td>
</tr>
<tr>
<td>Sokolow- Lyon (mm)</td>
<td>24 ± 9</td>
<td>25 ± 10</td>
<td>23 ± 8</td>
<td>0,611</td>
</tr>
</tbody>
</table>

After comparing patients' EKG characteristics before treatment and on day 14 of randomization, an increase in QTc interval on D14 from 411 ± 41 to 418 ± 37 ms was observed as well as a PR space increase from 169 ± 25 to 177 ± 3 6 ms (Table 3).

**Table 3. EKG patterns at inclusion and on day 14 of randomization.**
<table>
<thead>
<tr>
<th>Variable</th>
<th>ΔJ14-J1</th>
<th>Day 1</th>
<th>Day 14</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (per minute)</td>
<td>0,820</td>
<td>78 ± 13</td>
<td>79 ± 12</td>
<td>0,343</td>
</tr>
<tr>
<td>P wave (ms)</td>
<td>1,010</td>
<td>114 ± 11</td>
<td>115 ± 13</td>
<td>0,314</td>
</tr>
<tr>
<td>PR space (ms)</td>
<td>8,232</td>
<td>169 ± 25</td>
<td>177 ± 36</td>
<td>0,001</td>
</tr>
<tr>
<td>QRS complex (ms)</td>
<td>0,469</td>
<td>76 ± 13</td>
<td>76 ± 13</td>
<td>0,560</td>
</tr>
<tr>
<td>QTc interval (ms)</td>
<td>8,835</td>
<td>404 ± 30</td>
<td>413 ± 35</td>
<td>&lt; 0,00</td>
</tr>
<tr>
<td>T wave (ms)</td>
<td>3,867</td>
<td>193 ± 31</td>
<td>197 ± 42</td>
<td>0,197</td>
</tr>
<tr>
<td>Sokolow- Lyon (mm)</td>
<td>0,004</td>
<td>24,5 ± 8,9</td>
<td>24,5 ± 8,5</td>
<td>0,990</td>
</tr>
</tbody>
</table>

Four patients (1.5%) had QTc prolongation beyond 500 ms. All these patients (3.3%) were in the HCQ-AZT arm (Figure 1).

Five patients (1.9%) had an increase greater than 80 ms. All these patients (4.0%) were in the HCQ-AZT group (Figure 2).

No patient in the Doubase C arm had a QTc prolongation of > 500 ms or an increment of >80 ms. No ventricular arrhythmias or torsade de pointes were observed. No sudden death was noted.

**Discussion**

The present study was conducted as part of the Doubase C versus HCQ-AZT clinical trial to evaluate the cardiac safety of two therapeutic strategies used to manage COVID-19.

**General characteristics of study participants**

Patients in our study had a mean age of 41 ± 15 years. Bepouka B et al. at the CUK CTCO found a mean age of 49 (16). The difference is partly explained by the fact that in our study, we selected only patients with mild and moderate COVID-19, while Bepouka B et al. included patients regardless of disease stage. Critical and severe forms of the disease are more common in older patients. Nlandu Y et al. found an average age of 55.6 years among hospitalized patients with severe and critical forms of COVID-19 in a private clinic in Kinshasa (16).

Regarding medical history, most participants did not have more than one comorbidity. Hypertension accounted for 14%, diabetes mellitus for 4%, HIV for 1%, and asthma for 3%. Inclusion criteria might have
influenced these results as patients with the severe/critical form who are more likely to bear comorbidities were excluded.

**Incidence of QTc prolongation**

The present study showed an incidence of QTc interval and QTc prolongation in the whole group of 1.5% and 1.9%, respectively. This result is low compared with data reported in Western countries (18, 19). This could be explained by the fact that we excluded patients with comorbidities who are likely to have QTc prolongation either because of underlying conditions or the adverse effects of several drugs they are taking. Nicholas et al. in the USA showed that the likelihood of prolonged QTc $\geq$ 500 ms was higher with concomitant administration of a loop diuretic (7).

Considering the QTc threshold at risk for major arrhythmia, the study showed that the HCQ-AZT treatment strategy prolongs the QTc interval in a statistically significant manner compared with Doubase C. Indeed, four patients (3.3%) in the HCQ-AZT arm showed QTc prolongation beyond 500 ms and five patients in the same group showed a QTc increase of at least 80 ms. In contrast, no patient in the Doubase C arm showed any increase. Brian et al. revealed in an observational study in New York City a frequency of QTc $\geq$ 500 ms of 22% in a sample of 105 patients (4). Another study at New York University found a high prevalence of QTc $\geq$ 500 ms at 11% in a sample of 84 patients (17). In France, a study reported 33% of patients with QTc $\geq$ 500 ms in a total of 18 patients who were treated with HCQ-AZT (9). In Italy, Andrea Bernardini et al. found a QTc prolongation in 61% of patients (for a total of 117 patients) treated with HCQ alone or in combination with AZT. However, only four (4%) had a QTc $\geq$ 500 ms (15).

Overall, studies conducted in western countries have reported a higher occurrence of QTc prolongation than the present study. This difference could be explained first by the delay in performing EKGs after treatment, which was four days for patients in the HCQ-AZT arm (treatment for ten days and control EKG performed on D14) versus seven days for the Doubase C arm (treatment for seven days and control EKG performed on D14). In the studies cited above, EKGs were generally performed every other day. Secondly, the difference in HCQ and AZT dosages and the duration of treatment could explain the difference in the incidence of prolonged QTc between studies. It is described that QTc prolongation due to HCQ alone or in combination with AZT is dose-dependent and concentration-dependent (6). As for Doubase C, a relatively new molecule, there are few studies to our knowledge that have evaluated QTc prolongation incidence. Future studies are needed.

**Incidence of other EKG abnormalities**

No malignant cardiac arrhythmias (torsade de pointes, ventricular fibrillation) or sudden deaths were observed among study participants. In contrast, in France, the pharmacovigilance center reported 7 cases of sudden death, not to mention syncope due to excessive prolongation of the QTc interval, in 43 patients treated with HCQ alone or in combination (18). However, some observational studies have also failed to demonstrate an association between HCQ-AZ and the QTc prolongation increasing the risk of transition to torsade de points (19, 20). This may suggest that the actual risk of transition to torsade de pointes in this setting is low. A 2018 systematic review found no events in 1,702 subjects who received CQ in a
malaria endemic setting (21). Although HCQ has a known influence on the QTc interval, potentially leading to torsade, reports of arrhythmia-related deaths under WHO monitoring in malaria or systemic lupus erythematosus are lacking.

**Strengths and limitations**

The present study is the very first clinical trial in the DRC to show QTc prolongation in a few patients with mild to moderate COVID-19 treated with HCQ-AZT. Comparing the safety of two therapeutic strategies used in DRC shows that the HCQ-AZT combination presents a cardiac risk but at a lower level compared to studies in western countries. The cardiac safety reported in the Doubase C arm encourages further research in herbal medicine.

Nevertheless, there are limitations to the interpretation of the results. EKGs were obtained four days after the end of treatment for the HCQ-AZT arm and seven days after treatment for the Doubase C arm. Renal clearance might have reduced blood concentration and thus cardiac effects. Ideally, an EKG should be obtained daily, or a Holter EKG should be available.

**Conclusion**

Cardiac complications (QTc prolongation) are uncommon in Congolese patients treated with HCQ-AZT for mild to moderate COVID-19. Unlike Doubase C, the HCQ-AZT strategy presents a risk of QTc prolongation.

**Declarations**

**Ethics approval and consent to participate**

All experiments were performed in accordance with relevant guidelines and regulations of the Declaration of Helsinki. Our research project had been authorized by the Kinshasa School of Public Health (ESP/CE/038/2021). Informed consent was obtained from all patients to participate in the study. Data were fully anonymized before being accessed.

**Consent for publication**

Participants gave their consent to publish study results.

**Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare no conflict of interest.
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Authors contributions

B.M., JR.M. and B.L. conceived the idea, designed and supervised the study, had full access to all data and drafted the first version of manuscript. A.N. performed statistical analysis and. All authors participated in the production of the Doublease C molecule; They revised the manuscript and approved the final submitted version for publication and have agreed to be accountable for all aspects of the work.

Acknowledgments

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References


Figures

Figure 1

incidence of QTc interval $\geq 500$ ms
Figure 2

incidence of increment ≥ 80 ms at D14 of randomization