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Cardiac Safety of Hydroxychloroquine-Azithromycine for COVID-19 Patients: Pandemic Experience of Military Teaching Hospital of Rabat

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Abstract **Original Research Article**

Introduction: While recent studies are still arguing the efficacy of Hydroxychloroquine and Azithromycin to heal patients with SARS-CoV-2 infection, Moroccan's ministry of health has decided to maintain the protocol using these drugs. The main objective of this study is to characterize the degree and risk of QT prolongation in patients with COVID-19 in association with their use. ***Methods*:** This study is a cohort performed at Mohammed V Military Hospital of Rabat, of patients hospitalized with at least 1 positive COVID-19 nasopharyngeal reverse transcriptase polymerase chain reaction (RT-PCR) test result, and who received 10 day of hydroxychloroquine with 7 days of azithromycin from May9 through May26, 2020. Hydroxychloroquine was given orally at 200 mg TID. Azithromycin was given at a dose of 500 mg the first day followed by 250 mg daily for 6 days. Electrocardiogram was performed before the prescription, 2 days after and at the end of treatment. ***Results*:** During this period, 327 ECGs were studied, representing 109 unique patients. Their median age was 30 [25.5-44] years and 100% were male. All patients developed a paucisymptomatic form of the virus. Tisdale score varied between 6 and 8 points (89.9%-10.1%). The difference ΔQTc was significant ($p<0.01$) from day 0 to 10 with a ΔQTc of 16.15 ms. However, the maximal QTc hadn't exceed 500 milliseconds. None of the patients developed torsades de pointes or any other ventricular arrhythmias. ***Conclusion:*** Moroccan experience can reassure the prescribers on the safety of use of this drug combination in the threatening epidemic context.

Keywords: Hydroxychloroquine-Azithromycine, Covid-19 Patients, Pandemic Experience.

INTRODUCTION

While recent studies are still arguing the efficacy of Hydroxychloroquine and Azithromycin to heal patients with SARS-CoV-2 infection, Moroccan's ministry of health has decided to maintain the protocol supported earlier by the Chinese and Marseille's studies despite the concerns raised by the World Health Organization. However, these medications carry their own risks in spite of their being non prohibitive for multiple uses. In fact, combining these medications at unusual higher doses in the setting of a mystifying illness with a pro-inflammatory state, has given cause of concerns about a risk of QT prolongation and arrhythmia.

OBJECTIVE

The main objective of this study is to characterize the risk and degree of QT prolongation in patients with COVID-19 in association with their use of hydroxychloroquine combined with azithromycin.

METHODS

The study is a cohort performed at Mohammed V Military Teaching Hospital of Rabat, of patients hospitalized with at least 1 positive COVID-19 nasopharyngeal reverse transcriptase polymerase chain reaction (RT-PCR) test result who received 10 day of hydroxychloroquine combined with 7 days of azithromycin from May9 through May 26, 2020.

Hydroxychloroquine was given orally at 200 mg TID. Azithromycin was given orally at a dose of 500 mg the first day followed by 250mg daily for 6 days. In addition, patients were given adjuvant treatment such as vitamin C, D and Low molecular weight heparin at a preventive dose.

Electrocardiogram (ECG) monitoring was performed at Day0 before the prescription, 2 days after and at the ending of treatment.

ECGs were manually evaluated by cardiologists to calculate QT from either lead II, V2 or V5 of the 12-lead ECG when heart rate is between 60 and 80 bpm, and corrected using the Bazett formula when it's not in the interval below or the Fridericia formula when heart rate is beyond 100; before any intraindividual or interindividual QTc comparisons are made.

The QT interval was measured using the "Tangent" method [1]. QT measurements were validated when necessary by a senior electrophysiologist.

The Tisdale score was applied at the admission of patients to evaluate QTc prolongation risk. Physiological factors that may prolong the QT were searched for each admitted patient, in addition to concomitant take of QTc-prolonging drugs. Patients were questioned about symptoms or familial history that can suggest the presence of a congenital long QT syndrome.

Potassium level and kidney function were the two biological parameters studied. Symptoms like palpitations, diarrhea, nausea/vomiting or lipothymia/syncope were searched after the start of treatment.

STATISTICAL ANALYSIS

Statistical analysis was performed using IBM SPSS Statistics 26. Continuous variables are expressed as mean ± standard deviation, and categorical variables are expressed as percentages (95% confidence interval).

ANOVA with repeated measures was used to study the changes of electric parameters after the administration of treatment. A sphericity test of Mauchly was performed to see the significance of individual changes of corrected QT interval (QTc), PR interval, and heart rate. Multiple comparisons were adjusted by Bonferroni method.

RESULTS

During the 17 days period from May9 to May 26, 2020, we identified 327 ECGs that came from patients with a positive diagnosis of COVID-19, representing 109 unique patients.

The median age of our patients was 30 [25, 5-44] years and 100% were male. All patients developed a paucisymptomatic form of the virus, and all of them were enrolled outside the intensive unit care.

Physiological factors that may prolong the QT were searched for each patient. 41 patients (37.6%) had either obesity or overweight; 2 patients (1.8%) had dysthyroidism, 2 of them were alcoholic and 3(2.8%) had a history of central nervous system damage. None of the patients had an underlying cardiovascular disease or wore an implantable medical device. Loop diuretics were not taken by any of the patients, and none of the concomitant medications (which were taken by a very few of the patients) were among the QT prolonging drugs.

None of the patients experimented syncope in their past or had a family history of sudden death. However, one of the 109 patients (0.9%) had a congenital deafness.

None of the patients had been admitted for sepsis nor heart failure or acute myocardial infarction. The only two QTc-prolonging medications were hydroxychloroquine and azithromycin they were about to take, only 8 patients (7.3%) had a low potassium level $\leq$3.5 mmol/l with the least value of 3.3mmol/l. 3 (2.75%) of the patients had a baseline QTc $\geq$450ms. Cumulative Tisdale score varied between 6 and 8 points (89.9%-10.1%) enrolling patients between low and moderate risk.

The mean (SD) baseline QTc was 377±29.46 milliseconds with a maximal value of 472ms. At day 2 of treatment, QTc was 383±24 and at the last day of treatment 393±28 with a maximal value of 475ms. (Figure1-2)

The difference ΔQTc was significant ($p<0.01$) from day 0 to 10 with a ΔQTc of 16.15 ms, and from day 2 to 10 with a ΔQTc of 9.7 ms (p0.003). However, the maximal QTc hadn't exceed 500 milliseconds, thus none of the patients had to discontinue hydroxychloroquine and azithromycin. In fact, none of them developed torsades de pointes or any other ventricular arrhythmias. (Figure3)

The mean (SD) PR interval was 161±18 with a maximal of 208 ms before therapy, 165±19 with a maximal of 220 ms 2 days after, and 167±22 with maximal PR of 260 at the end of therapy (Figure5). The difference ΔPR was significant (p.004) from day 0 to 10 with a ΔPR of 5.49ms, and from day 0 to 2 with a ΔPR of 4.09 ms (p.018) (Figure4). Medications were not discontinued for patients with first degree block.

After the beginning of therapy with hydroxychloroquine and azithromycin, ECG showed a

stable heart rate (69±11day10 vs 68±13 day2 vs 68±14 day0 beats/min).

3 of our patients developed partial right bundle branch block. Side effects of treatment such as diarrhea; nausea/vomiting and palpitations were reported respectively in 33%, 2.8%, and 12.8% of our patients resolving spontaneously in several days.

Table-1: Clinical characteristics of COVID-19 patients under treatment with hydroxychloroquine and azithromycin (total=109)

Characteristics	No. (%)
Age, median (IQR)	30 [25.5-44]
Male effective (percentage)	109 (100%)
Obesity, overweight	
Yes	41(37.5%)
No	68 (62.4%)
Dysthyroidism	
Yes	2 (1.8%)
No	107 (98.2%)
Alcoholism	
Yes	2 (1.8%)
No	107 (98.2%)
Central nervous system damage	
Yes	3 (2.8%)
No	106 (97.2%)
Serum creatinine, mg/l (mean, SD)	8±1.07
Creatinine Clearance/min/1.73m2, MDRD equation, (mean, SD)	107±15.43
Potassium level	8 (7.3%)
<3.6 mmol/l	101(92.7%)
3.6-5.3 mmol/l	
	377±29.46
Baseline QTc	
	31 (28.4%)
Baseline heart rate	56 (51.4%)
<60	20 (18.3%)
60-80	2 (1.8%)
80-100	
>100	102 (93.6%)
	7 (6.4%)
Baseline PR	
120-200ms	17 (15.6%)
>200ms	92 (84.4%)
Left ventricular hypertrophy	33 (30.3%)
Yes	76 (69.7%)
No	
Bundle block before treatment	85 (78%)
Yes	22 (20.2%)
No	1 (0.9%)
QRS	98 (89.9%)
<100	11 (10.1%)
100-120	
>120	
Tisdale Score at treatment initiating	
Low risk	
Moderate risk	383±24.25
Day 2	99 (90.8%)

QTc	10 (9.2%)
PR	
120-200ms	
>200ms	26 (23.9%)
	67 (61.5%)
Heart rate	15 (13.8%)
	1 (0.9%)
<60	
60-80	
80-100	
>100	393±28.85
	97 (89%)
Day 10	12 (11%)
QTc	
	18%
PR	75%
120-200ms	14%
>200ms	2%
Heart rate	
<60	36 (33%)
60-80	73 (67%)
80-100	
>100	
	3 (2.8%)
Posttreatment:	106 (97.2%)
Diarrhea	
Yes	14 (12.8%)
No	95 (87.2%)
Nausea or vomiting	
Yes	
No	
Palpitations	
Yes	
No	

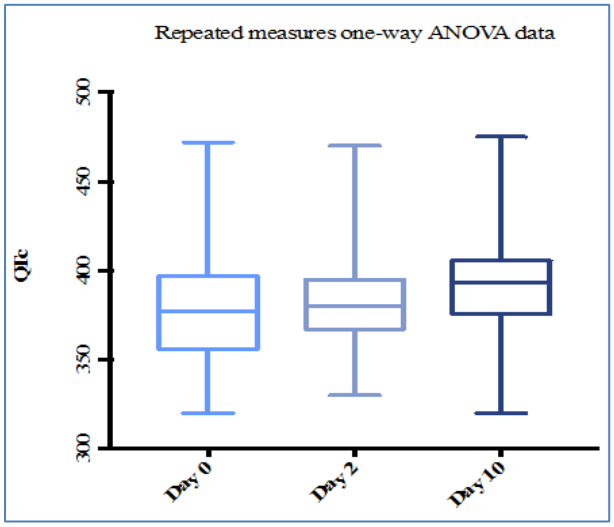

Fig-1: Evolution of corrected QT interval before the beginning (Day0), 48hours after (Day2) and at the end (Day10) of therapy with hydroxychloroquine and azithromycin. Repeated measures one-way ANOVA data

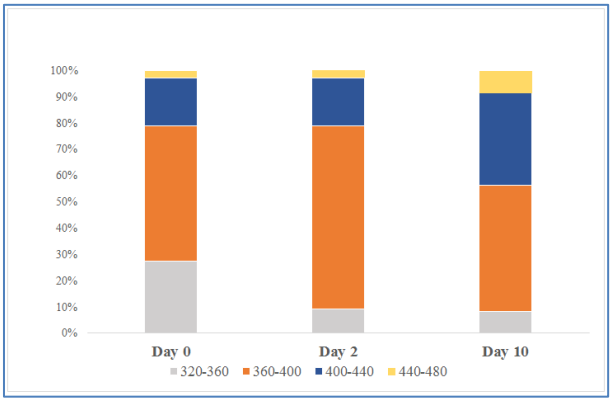

Fig-2: Distribution of corrected QT interval of the three days ECG according to intervals

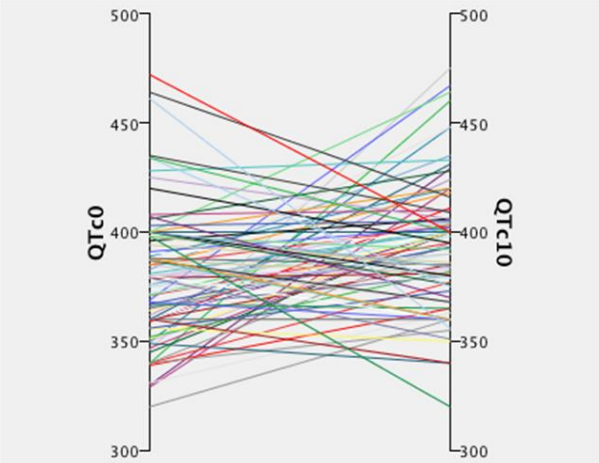

Fig-3: Individual changes in corrected (QTc) interval before the beginning (QTc0) and at the end (QTc10) of therapy with hydroxychloroquine and azithromycin

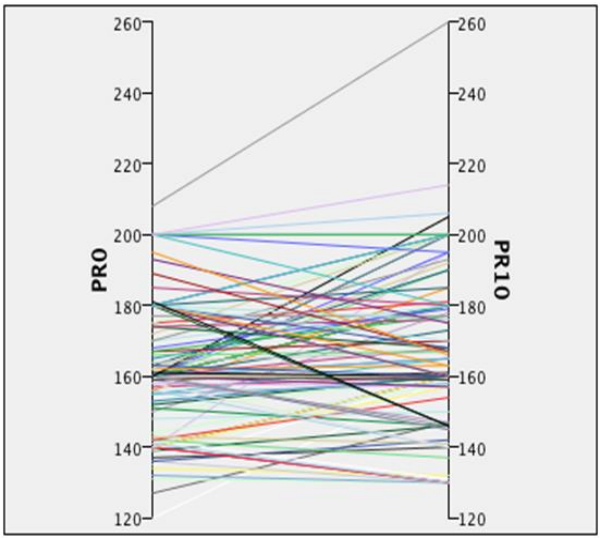

Fig-4: Individual changes in PR interval before the beginning (PR0) and at the end of therapy (PR10) with hydroxychloroquine and azithromycin

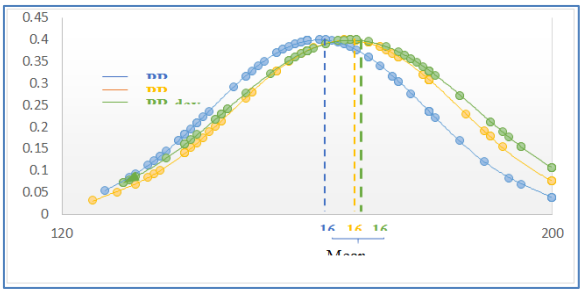

Fig-5: Distribution of PR interval density of day 0, day 2, and the end of treatment (day10)

DISCUSSION

Mechanism of action of Hydroxycholoroquine and Azithromycin in COVID19 infection

Hydroxychloroquine has been used as prophylactic pharmacotherapies for Plasmodium falciparum, and as first line antimalarial agents for Plasmodium ovale and Plasmodium vivax. It has also been used for the management of conditions such as systemic lupus erythematosus and rheumatoid arthritis. It has been hypothesized, based on in vitro data, that hydroxychloroquine may have therapeutic efficacy in the COVID-19 pandemic by inhibiting angiotensin-converting enzyme 2–mediated viral entry, and attenuating the post-viral cytokine storm observed in severe COVID-19 cases via a multitude of immunomodulatory mechanisms.

Azithromycin is a class of antibiotics known as macrolide. It is used to treat infections like bronchitis and pneumonia. With the spread of the SARS-CoV-2 viral pneumonia, researchers proved that azithromycin acted as an acidotropic lipophilic weak base which modulate the pH of endosomes and trans-Golgi network. This further led to in vitro effects on intracellular organelles similar to the one as conferred by hydroxychloroquine [2].

Cardiotoxic effects of drugs

a) Hydroxychloroquine HCQ

HCQ has been shown to be cardiotoxic due to lysosomal dysfunction and accumulation of glycogen and phospholipids(3). Their cardiotoxic effects appear to be related to the cumulative dose. In fact, high cumulative doses of HCQ have been shown to be associated with atrioventricular blocks and cardiac arrest [4, 5]. Sick sinus syndrome and QT prolongation have also been reported with high doses [5, 6]. In some of these cases, baseline QT interval was found to be mildly prolonged and hence QT interval is such patients should be closely monitored to prevent risk of ventricular arrhythmias. In our study, 2.75% of our patients had a baseline QTc ≥450ms and were asked to alert doctors in charge of the slightest symptom to perform control ECG.

HCQ is structurally and mechanistically similar to the class IA antiarrhythmic quinidine, which inhibits voltage-gated sodium and potassium channels, prolonging the QT interval and increasing the risk of torsades de pointes and sudden cardiac death. Given the fact that hypokalemia causes prolongation of QTc interval, low potassium levels in patients with severe COVID-19 may further exacerbate the arrhythmogenic potential of HCQ. 7.3% of our patients had a potassium level <3.6mmol/l, but none of them had experimented any kind of arrythmia. In a study of 85 patients treated with HCQ for a minimum of 1 year and who had no underlying cardiac disease, HCQ was found to be safe with only two patients developing right bundle branch block and one patient developing left bundle branch block [7]. There were no instances of atrioventricular blocks or QT prolongation. In our study, patients were under hydroxychloroquine combined with azithromycin as a treatment of SARS Cov-2 infection which make comparisons of results difficult. Nonetheless, it's important to mention that 3 of our patients developed a

partial right bundle branch block. A first-degree atrioventricular block was revealed in 5 of our patients.

b) Azithromycin

Initially thought to be free of cardiotoxic effects, it was later found to cause QT prolongation and higher risk of cardiovascular morbidity and mortality. Multiple studies have shown the risk of QT prolongation and ventricular tachycardia with azithromycin. Its use has also been linked to risk of atrial fibrillation and cardiac arrest. In a large multinational case-control study, azithromycin use was found to be associated with an increased risk of ventricular tachycardia [8]. However, in a large Canadian cohort, azithromycin use was not associated with risk of ventricular arrhythmia [9]. The mechanisms by which azithromycin causes arrhythmias are still under investigation. QT prolongation and ventricular arrhythmias have been postulated to be due to increased Na^+ current and inhibition of outward flow of K^+ ions from ventricular myocytes [10].

c) Combination of HCQ and Azithromycin

In a cohort of 84 hospitalized patients treated with hydroxychloroquine and azithromycin [11]. QTc increased from a mean baseline of 435 ms to a maximum of 463 ms after 3.6 days, with approximately 12% developing a QTc > 500 ms, a known marker of high arrhythmic risk. In parallel, our data showed that QTc increased from a mean baseline QTc of 377±29.46 milliseconds with a maximal value of 472ms to 393±28 at the last day of treatment with a maximal value of 475ms with a significant ($p<0.01$) ΔQTc of 15 ms from the pre-prescription to the ending of the association Hydroxychloroquine and Azithromycin.

This study also noted that baseline QTc poorly predicted this outcome, and that acute renal failure was the strongest predictor of developing acquired long QT syndrome [11-13]. In our cohort, the kidney function was evaluated for each patient based on clearance of creatinine. None of our patients was having an acute renal failure.

In COVID-19 patients, however, approximately 10% of patients developed QT prolongation to a degree that generally leads to the drug being withdrawn (QTc ≥ 500 ms or change > 60 ms) [14]. A case series of COVID-19 patients performed by Ramireddy and colleagues showed greater QTc prolongation with hydroxychloroquine and azithromycin (17 ± 39 ms) relative to azithromycin alone (0.5 ± 40 ms) [14]. In our study, Covid-19 positive patients were under both medications and each patient served as his own control, nevertheless no discontinuation of the treatment was indicated.

d) Arrythmias in COVID

One study of 40 intensive care unit patients in France treated with hydroxychloroquine 200 mg twice daily for 10 days (with or without azithromycin) noted that 14 (36%) developed QT prolongation, albeit with no arrhythmias reported [15].

However, another recent study of 90 hospitalized COVID-19 patients reported an event of torsades de pointes in a patient given hydroxychloroquine and azithromycin[16].

This event occurred three days after these drugs were discontinued, and other risk factors were present, such as bradycardia, new-onset cardiomyopathy, and use of propofol, a drug that is considered a known risk factor for torsades de pointes [14].

In the current study, COVID-19 patients receiving combined therapy with hydroxychloroquine and azithromycin did not experience any arrhythmic complications such as syncope or life-threatening ventricular arrhythmias, during the hospital stay. It has to be noted that Tisdale score at the initiation of treatment showed a low or moderate risk for all of our patients.

A Marseilles study showed that out of a significant number of pre-prescription electrocardiograms (over 500), treatment has only been contraindicated in exceptional cases. The treatment was then stopped for cardiovascular reasons only more exceptionally. Strict monitoring of patients by Professor Raoult's team did not reveal any significant clinical event. The results of our study corroborate perfectly with Raoult's ones. Treatment hadn't been contraindicated for none of the patients. ECG monitoring and close clinical monitoring didn't attest any major changing that may lead to drugs withdrawal.

Circumventing the QTc-Prolonging and torsadogenic potential of the association of hydroxychloroquine and azithromycin

Published guidance documents vary in their recommendations for monitoring and managing the potential adverse effects of possible pharmacotherapies for coronavirus disease 19, particularly the association of hydroxychloroquine and azithromycin.

A recent study [11] recommend daily ECG monitoring, with reassessment of the therapy if high risk markers appear (QTc >500 ms or ΔQTc > 60 ms). In this study, only partial resolution of the QTc was observed at 3 days after completion of therapy. This may be attributed to the prolonged half-life of Hydroxychloroquine. This finding, according to Chorin & al, requires special attention when considering discharging patients receiving HCQ/AZ or if outpatient treatment with HCQ/AZ is planned.

Other teams [17] performed 12-lead ECGs and 12-lead 24-h Holter ECG monitoring in all patients aged <80 years admitted to our medical unit for COVID-19, in oral therapy with hydroxychloroquine (200 mg, twice daily) and azithromycin (500 mg, once daily) for at least 3 days. Their data showed that patients with COVID-19 had QTc-interval 1) longer than controls during the whole day, and 2) stable over the 24-h, with no differences between different times of the day. Temporal stability of drug effects may be explained by the large volume of distribution with tissue accumulation and the long half-life of both medications [18, 19]. Their data support the need of a periodic, not daily, QTc surveillance in COVID-19 patients on treatment with hydroxychloroquine and azithromycin, in order to reduce personnel exposure risk and personal protective equipment consumption [20].

In our study we have opted for ECG monitoring at Day0 before the start of medications, 48 hours after and at the ending of treatment.

CONCLUSION

The ongoing pandemic coronavirus disease 2019 has led to several changes in clinical processes to achieve optimal care.

While the use of hydroxychloroquine and azithromycin is triggering a worldwide controversy and while studies are divided between its efficacity and its cardiovascular side effects, Moroccan experience, can reassure the prescribers on the safety of use of this drug combination in the threatening epidemic context, especially for young patients who don't have any underlying cardiovascular disease.

LIMITATIONS

This study has several limitations. The population in our study was military which we assume is young, with less comorbidity that may provide the QT prolongation. In addition, 100% of the patients were male; therefore the sex parameter was not studied. Finally, all patients were enrolled outside the intensive care unit and results may be different in critically ill individuals. Thus, applicability to other populations warrants further study.

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Consent: The authors confirm that consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance

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