ORIGINAL ARTICLE

Effects on QT interval of hydroxychloroquine associated with ritonavir/darunavir or azithromycin in patients with SARS-CoV-2 infection

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Abstract

Introduction Most of the drugs associations that have been used to treat patients with SARS-CoV-2 infection increase the risk of prolongation of the corrected QT interval (QTc).

Objective To evaluate the effects of an association therapy of hydroxychloroquine (HY) plus ritonavir/darunavir (RD) or azithromycin (AZ) on QTc intervals.

Methods At the beginning of COVID-19 pandemic patients admitted to our hospital were treated with the empiric association of HY/RD; one week later the therapeutic protocol was modified with the combination of HY/AZ. Patients underwent an ECG at baseline, then 3 and 7 days after starting therapy. We prospectively enrolled 113 patients (61 in the HY/RD group-52 in the HY/AZ group).

Results A significant increase in median QTc was reported after seven days of therapy in both groups: from 438 to 452 ms in HY/RD patients; from 433 to 440 ms in HY/AZ patients ($p = 0.001$ for both). 23 patients (21.2%) had a QTc > 500 ms at 7 days. The risk of developing a QTc > 500 ms was greater in patients with prolonged baseline QTc values (≥ 440 ms for female and ≥ 460 ms for male patients) (OR 7.10 (95% IC 1.88–26.81); $p = 0.004$) and in patients with an increase in the QTc > 40 ms 3 days after onset of treatment (OR 30.15 (95% IC 6.96–130.55); $p = 0.001$). One patient per group suffered a malignant ventricular arrhythmia.

Conclusion Hydroxychloroquine with both ritonavir/darunavir or azithromycin therapy significantly increased the QTc-interval at 7 days. The risk of developing malignant arrhythmias remained relatively low when these drugs were administered for a limited period of time.

Keywords COVID-19 · Hydroxychloroquine · Ritonavir · Darunavir · Azithromycin

Introduction

Starting from December 2019, an outbreak of viral respiratory illness named coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China, and spread rapidly worldwide as a pandemic [1]. Currently, no specific therapies are available for patients with SARS-CoV-2 infection and several drugs approved for other diseases are used in this context.

Hydroxychloroquine (HY) has been demonstrated to have an anti-SARS-CoV-2 activity in vitro [2]. Moreover, a recent study reported a significant viral load reduction in COVID-19 patients treated with hydroxychloroquine and this effect seemed to be reinforced by azithromycin (AZ) [3]. Based on this study, clinicians in many countries have begun to use these medications in clinical practice. It is generally used with the dosage of 200 mg b.i.d, but has often been evaluated in higher dosage as 600 mg per day [3–5].

Some retrospective studies suggested a potentially favorable effect of HIV protease inhibitors such as Darunavir in combination with Lopinavir in COVID-19 patients [6, 7]. According to this evidence, at the beginning of the outbreak, antiretroviral off-label use in COVID-19 patients was widespread [8], the results for some secondary endpoints are interesting and many studies conducted with antiviral therapy are ongoing.

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Hydroxychloroquine, azithromycin and ritonavir/daru-navir (RD) are generally well-tolerated but all three are associated with an increased risk of corrected QT (QTc) prolongation and cardiac arrhythmias [9–11] which may further increase when these drugs are administered together. However, safety data for these treatments, alone or in combination, are still lacking in COVID-19 patients. We evaluated the effects of hydroxychloroquine in combination with ritonavir/darunavir or azithromycin on QTc length and the risk of malignant arrhythmias in patients with COVID-19 pneumonia.

Methods

At the beginning of COVID-19 pandemic (March 2nd–8th, 2020) all of the patients with a confirmed diagnosis of SARS-CoV-2 pneumonia admitted to our hospital were treated with the empiric association of HY/RD, while the week later (March 9th–15th, 2020) the therapeutic protocol was modified by our internal ad hoc committee, and patients received the combination of HY/AZ.

Patients were included in the study if they had the following criteria: a confirmed clinical and radiological diagnosis of SARS-CoV-2 pneumonia, according to the criteria proposed by Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition, published online on March 4, 2020); positive Reverse-Transcriptase-Polymerase-Chain-Reaction (RT-PCR) assay for SARS-CoV-2 in a respiratory tract sample; electrocardiogram (ECG) recordings at baseline and then three and seven days after starting therapy; full treatment with the prescribed drugs for 7 days, unless onset of malignant ventricular arrhythmias.

Exclusion criteria were: QTc > 500 ms on baseline ECG, history of severe systolic dysfunction (left ventricular ejection fraction < 35%), history of arrhythmias, bradycardia < 50 bpm, concomitant drugs that could cause QTc prolongation or early interruption of the medical therapy due to side effects.

The drugs were given at the following doses: HY 200 mg b.i.d; RD 100/800 mg q.d.; azithromycin 500 mg q.d. Standard 12-lead ECG was recorded at screening time before the beginning of the therapy (day 0) and after three (day 3) and 7 days (day 7). Triplicate ECG collection was obtained at three time points to reduce noise of individual QT interval measurements. The QTc interval was calculated according to Bazett's formula ($QTc = QT \div \sqrt{RR}$) in the II lead or V5 lead. ECGs were independently evaluated and a manual adjudication of automated QTc interval measurements was done by two senior cardiologists (M.L. and L.M.). Significant changes in QTc (∆QTc) and development of prolonged QTc interval > 500 ms were reported in the whole cohort. Clinical and laboratory data were

recorded as far as in-hospital outcomes. The study was approved by our Ethical Committee.

Statistical analysis

Continuous variables were summarized as median with interquartile range (IQR) and compared with the Mann–Whitney U test and Wilcoxon matched pairs signed rank. Categorical variables were presented as number (%), and proportions for categorical variables were compared using the χ^2 or Fisher exact test as appropriate. Odds ratio (OR) was calculated using logistic regression. A two-sided $p < 0.05$ was considered statistically significant. Statistical analyses were done using the SPSS version 21.0 software (IBM, New York, USA).

Results

During the study period, a total of 137 patients were considered for treatment with the combinations of drugs. Twenty-four patients were excluded from the analysis: two had a severe systolic dysfunction; six history of arrhythmias and/or bradycardia < 50 bpm; five were chronically taken drugs that could cause QTc prolongation; 11 subjects were excluded for the appearance of drug-related side effects: ten complained of nausea and diarrhea and one referred dizziness. Finally, the study population consisted of 113 patients: 61 subjects in the HY/RD group, and 52 patients in the HY/AZ group.

Baseline characteristics and clinical outcomes

Clinical characteristics and laboratory tests of the two groups are reported in Tables 1 and 2. The most common comorbidities were hypertension (28%) and diabetes mellitus (14%); 61 patients (54%) needed non-invasive ventilation (34 in the HY/RD group and 27 in the HY/AZ group). Only one patient required mechanical ventilation.

In-hospital death occurred in 9 (8%) patients (7 in the HY/RD group and 2 in the HY/AZ group).

All of them died of acute respiratory distress syndrome or multi-organ failure. Ventricular arrhythmias were recorded in two cases (1.8%): one patient in the HY/RD group developed torsade de point (TdP) and ventricular fibrillation successfully treated with 200 J Direct-Current shock after 6 days of therapy and one patient in the HY/AZ group developed non-sustained ventricular tachycardia after 4 days. Both patients presented a QTc value > 500 ms and stopped the therapy.

Table 1 Clinical characteristics and in-hospital outcomes

Parameters	Total (n = 113)	HY/RD (n = 61)	HY/AZ (n = 52)
Age (years)	68 (61–74)	67 (61–74)	68 (60–74)
Gender (male)	85 (75%)	49 (80%)	36 (69%)
Hypertension	32 (28%)	18 (29%)	14 (27%)
Diabetes	16 (14%)	10 (16%)	6 (12%)
Smoking	10 (9%)	7 (11%)	3 (6%)
COPD	4 (4%)	2 (3%)	2 (4%)
Chronic kidney disease	6 (5%)	4 (7%)	2 (4%)
Atrial Fibrillation	8 (7%)	2 (3%)	6 (11%)
CAD	12 (11%)	7 (11%)	5 (10%)
NIV	42 (37%)	26 (43%)	16 (31%)
Intubation	1 (0.8%)	1 (1.6%)	0
Death	9 (8%)	7 (11%)	2 (4%)

Data are presented as median (IQR) or *n* (%); *HY* hydroxychloroquine, *msec* milliseconds, *COPD* chronic obstructive pulmonary disease *CAD* coronary artery disease, *NIV* non-invasive ventilation; *QTc* corrected QT interval, *ΔQTc* change in corrected QT interval

ECG evaluation

In the 111 patients who had taken the drugs for the entire length of the study, a statistically significant increase of QTc interval was reported at 7 days. A QTc interval > 500 ms was observed in 15 (13%) patients on day 3 and in 23 (20%) on day 7. In 18 (16%) patients, an increase in the QTc > 40 ms three days after onset of treatment was documented. At the univariate regression analysis, the risk of developing a QTc > 500 ms was greater in patients with prolonged baseline QTc values (≥ 440 ms for female and ≥ 460 ms for male) (OR 3.9 (95% CI, 1.47–10.17); *p* = 0.006) and in patients with an increase in the QTc > 40 ms three days after onset of treatment (OR 19.9 (95% CI, 5.93–66.44); *p* = 0.001) (Table 3). Impaired renal function in terms of estimated glomerular filtration rate < 60 ml/min/1.73mq was related to the risk of developing a QTc interval > 500 ms (OR 3.5 (95% CI 1.33–9.44), *p* = 0.012).

The multivariate regression analysis indicated that prolonged baseline QTc values (OR 7.10 (95% IC 1.88–26.81); *p* = 0.004) and the increase in the QTc > 40 ms three days after onset of treatment (OR 30.15 (95% IC 6.96–130.55); *p* = 0.001) were independent predictors of QTc prolongation (> 500 ms); estimated glomerular filtration rate < 60 ml/min/1.73mq was not significant (*p* = 0.6) (Table 3).

Hydroxychloroquine plus ritonavir/darunavir group

The QTc interval increased progressively overtime from 438 ms (421–454) at day 0 to 448 ms (429–483) at day 3 and to 452 ms (430–490) at day 7 (baseline vs. day 3, p = 0.001; baseline vs. day 7, p = 0.001; day 3 vs. day 7, *p* = 0.001) (Fig. 1).

Hydroxychloroquine plus azithromycin group

The QTc interval increased progressively overtime from 433 ms (412–447) at baseline to 430 ms (420–447) at 3 days and to 440 ms (428–464) at 7 days (baseline vs. day 7, *p* = 0.001) (Fig. 2).

Table 2 Laboratory data

Parameters	Normal range	HY/RD (n = 61)	HY/AZ (n = 52)
D-dimer (μg/ml)	0–0.5	2.4 (0.9–3.1)	2.3 (0.98–2.7)
Hs-TnI(ng/L)	0–34	12.7 (8.15–52.6)	3.6 (0.6–118)
CRP (mg/L)	0–5	51 (51–174)	56 (24–159)
WBC (*10^3/mm^3)	3.9–10.6	5.3 (3.8–8.1)	6.2 (4.8–8.3)
Potassium (mEq/L)	3.5–5	4 (3.8–4.1)	3.8 (3.7–4)
Sodium (mEq/L)	135–145	134 (134–138)	139 (134–140)
ALT (U/L)	0–41	25 (24–48)	25 (17–32)
AST (U/L	10–40	37 (37–50)	37 (33–60)
LDH (U/L)	< 248	345 (178–453)	232 (182–297)
Creatinine (mg/dL)	0.7–1.18	1 (0.99–1.3)	0.9 (0.75–1)
eGFR (ml/min/1.73mq)	> 60	59 (53–60)	63 (59–89)
Pa02 (mmHg)	80–100	64 (54–65)	64 (57–64)
Pa02/Fi02 ratio (mmHg/%)	> 300	305 (257–309)	304 (271–419)
S02 (%)	95–100%	94 (90–94)	94 (90–97)

Data are presented as median (IQR) or *n* (%). *hs-TnI* high sensitive troponin I, *CRP* C-reactive protein; *WBC* white blood cell count, *ALT* alanine aminotransferase, *AST* aspartate transaminase, *INR* international normalized ratio, *LDH* lactate dehydrogenase, *eGFR* estimated glomerular filtration rate, *Pa02* arterial oxygen partial pressure, *S02* oxygen saturation, *Fi02* fraction of inspired oxygen

Table 3 Predisposing risk factors for QTc interval prolongation (≥ 500 ms)

Parameters	Univariate analysis		Multivariate analysis	
	QTc ≥ 500 ms OR (95% CI)	*p* value	QTc ≥ 500 ms OR (95% CI)	*p* value
Baseline QTc prolongation (≥ 440 ms female, ≥ 460 ms male)	3.86 (1.47–10.17)	0.006	7.10 (1.88–26.81)	0.004
Delta QTc > 40 ms (0–3 days)	19.86 (5.93- 66.44)	0.001	30.15 (6.96- 130.55)	0.001
eGFR < 60 ml/min/1.73mq	3.53 (1.32–9.44)	0.012	1.38 (0.41–4.67)	0.600
Non-invasive ventilation	0.43 (0.17–1.08)	0.072		
CRP > 50 mg/L	1.40 (0.47–4.18)	0.543		
Baseline serum K < 3.8 mg/dL	0.68 (0.22–1.89)	0.417		
Baseline serum Na < 138 mg/dL	1.71 (0.68–4.30)	0.259		

QTc corrected QT interval, *eGFR* estimated glomerular filtration, *CRP* C-reactive protein
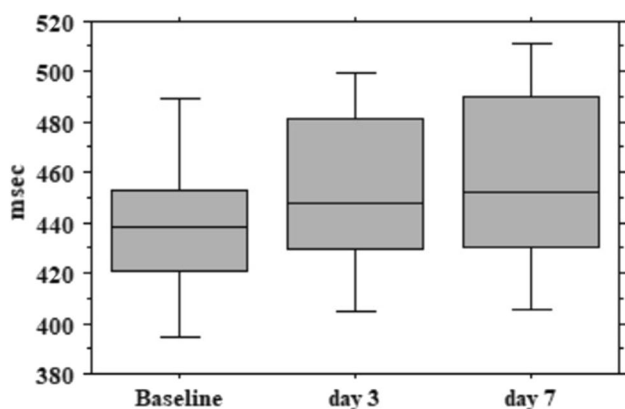
Fig. 1 QTc interval trend (minimum, first quartile, median, third quartile and maximum) at baseline, day 3 and day 7 in hydroxychloroquine plus ritonavir/darunavir group
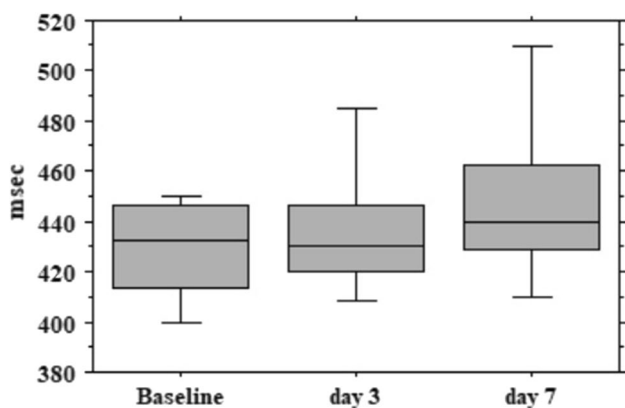
Fig. 2 QTc interval trend (minimum, first quartile, median, third quartile and maximum) at baseline, day 3 and day 7 in hydroxychloroquine plus azithromycin group

Discussion

Drug-induced QT prolongation is considered a surrogate indicator for increased risk of drug-associated TdP [12]. Although only a small proportion of patients with QTc prolongation suffer from TdP, drug-associated QT prolongation is related to increased arrhythmic and non-arrhythmic mortality [13, 14]. Hydroxychloroquine and azithromycin are known to induce QTc prolongation directly by blocking inward cellular potassium current and indirectly by inhibiting CYP2D6 and therefore increasing the circulating levels of eventual concomitant drugs that prolong QTc, which can promote life-threatening ventricular arrhythmias [15, 16]. Ritonavir is a protease inhibitor developed for the treatment of HIV infection used in combination with other antiretroviral drugs such as lopinavir or darunavir. A recent trial reported a QT prolongation in COVID-19 patients treated with ritonavir and lopinavir but no pro-arrhythmic adverse events were observed [9]. However, ritonavir is a potent CYP3A4 inhibitor and hence its potential pro-arrhythmic risk. These drugs are generally well tolerated when used in chronic diseases, but data about their safety came mainly from in vitro studies and small non-randomized clinical trials. Evidence about their use alone or in combination in an acute setting such as COVID-19 pneumonia is still limited. COVID-19 patients are likely to have longer baseline QTc as a result of the metabolic and physiologic sequelae of their illness and particularly they are exposed to a systemic inflammatory response, electrolyte imbalance and concomitant drugs leading to an increased risk of QTc prolongation [17]. All these factors could increase the risk of adverse drug effects related to the use of hydroxychloroquine, especially in combination with ritonavir/darunavir or azithromycin [18, 19]. Our study reported a significant prolongation of

QTc interval at 7 days in patients with severe COVID-19 pneumonia treated with hydroxychloroquine with both combinations. This prolongation of QTc was already present at 3 days after the onset of treatment in the HY/RD group.

Moreover, during the study period, 20% of our patients developed a QTc > 500 ms. The risk of developing a QTc interval > 500 ms was greater in patients presenting with a QTc prolongation at baseline and in those with an increase in the QTc interval > 40 ms compared with the pre-drug baseline values. This value is a more stringent criterion compared to the one reported by the current guidelines on the prevention of TdP that used to consider significant interval of least 60 ms [15]. In our population, we observed two cases (1.8%) of ventricular arrhythmias (one of TdP and another of recurrent episodes of non-sustained ventricular tachycardia) both in patients with a QTc > 500 ms. While the risk of developing malignant arrhythmias remains relatively low in a short period of administration, our observations confirm the safety concerns raised by two recent studies about the use of hydroxychloroquine in COVID-19 patients [18, 19]. Because of this evidence, every patient hospitalized for COVID-19 should be subjected to a careful assessment of baseline risk of QT prolongation, including baseline ECG, laboratory exams, and collection of medical and pharmacological history to identify and to correct potentially arrhythmogenic risk factors such as electrolyte disturbances or concomitant use of QTc prolonging agents [20]. In our experience, impaired renal function (estimated glomerular filtration rate < 60 ml/min/1.73 mq) and the need for non-invasive ventilation were not associated with the risk of developing a QTc > 500 ms. These findings seem to suggest that the prolongation of the QTc was not related to the characteristics associated with the severity of the underlying disease and the clinical course.

The design of the study does not allow a comparison between groups: however, in HY/RD group the QTc seemed to increase to higher values than in HY/AZ group. Further studies are needed to understand if the combination HY/RD should be regarded as a less convenient option for the higher risk of QTc prolongation.

In conclusion, in patients with COVID-19 pneumonia treated with hydroxychloroquine in association with antiviral drugs ritonavir/darunavir or azithromycin, a close QTc surveillance should be performed especially in high-risk patients such as those who present a QTc prolongation at baseline or those who experienced an increase in the QTc > 40 ms compared with the pre-drug value. This close monitoring would allow the prompt identification of subjects with increased pro-arrhythmic risk in which discontinuation of the treatment should be considered after a careful evaluation of the risk/benefit of the ongoing therapy.

Limitations

This study has several limitations. First, the sample size is relatively small. Second, the study population consisted of two consecutive series of patients with different characteristics that do not allow a comparison between groups. Moreover, we do not have a control group of treatment with only hydroxychloroquine. Finally, higher risk subjects may not have been represented in our population because we excluded individuals with prolonged QTc intervals at baseline as recommended by international guidelines.

Compliance with ethical standards

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