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CASE REPORT
Arrhythmias/electrophysiology

Drug-induced 'Torsade de Pointes' in a COVID-19 patient despite discontinuation of chloroquine. Importance of its long half-life: a case report

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Background Early studies have led to the repositioning of a subgroup of antimalarial agents (e.g. chloroquine and hydroxychloroquine) as antiviral treatment in coronavirus disease 2019 (COVID-19) patients. These drugs are now being prescribed based on small non-controlled studies, but larger controlled studies have yet to demonstrate the positive effect of these drugs. In addition, these drugs are also known for their QT interval-prolonging effect associated with significant morbidity and mortality.

Case summary We present a case of a 66-year-old female admitted to the intensive care unit with respiratory failure due to COVID-19. She was treated with chloroquine (QTc interval at baseline was 429 ms). Despite cessation of chloroquine, but after the start of erythromycin, she developed severe QTc interval prolongation (QTc interval 550 ms) and 'Torsade de Pointes'. Two weeks after cessation of all QTc interval-prolonging drugs, the QTc interval was restored.

Discussion The elimination half-life of chloroquine ranges from days up to weeks. Even after discontinuation of chloroquine, ECG monitoring in COVID-19 patients is warranted. We recommend observation of the QT interval after cessation of chloroquine in cases where other potentially QT interval-prolonging drugs are introduced.

Keywords COVID-19 • Coronavirus • SARS-CoV-2 • Chloroquine • QT interval prolongation • Torsade de Pointes • Case report

Learning points

- To understand the QT-prolonging effects and long half-life of chloroquine.
- We recommend observation of the QT interval after cessation of chloroquine, in cases where other potentially QT interval-prolonging drugs are introduced.

Introduction

At the end of 2019, a new variant coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan, Hubei, China[1] and caused an outbreak of coronavirus disease 2019 (COVID-19). Extensive efforts in finding an effective treatment for symptomatic patients have led to the repositioning of known drugs for possible use as antiviral treatments. In the early

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stages of the pandemic, clinical non-randomized controlled trials showed that chloroquine had a significant effect regarding clinical outcome and viral clearance in COVID-19 patients.[2] This has led to the worldwide distribution of this drug as treatment for COVID-19. However, a recent study demonstrated that the use of this drug was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias when used for treatment of COVID-19.[3] We present a case of severe QT interval prolongation leading to 'Torsade de Pointes' (TdP) in a COVID-19 patient in the intensive care unit (ICU).

Timeline

Day 1	A 66-year-old female is admitted to the internal medicine ward with COVID-19
	Due to her medical condition, the patient was treated with chloroquine; QTc interval at baseline was 429 ms
Day 3	Due to respiratory failure, the patient was transferred to the intensive care unit for mechanical ventilation
Day 5	Chloroquine treatment was discontinued due to QTc prolongation; QTc interval was 482 ms
Day 6	Erythromycin was initiated to improve gastric motility; QTc interval was 453 ms
Day 7	The patient was resuscitated due to 'Torsade de Pointes'; QTc interval was 522 ms
	Erythromycin treatment was discontinued
Day 15	8 days after cessation of all QTc-prolonging drugs; QTc interval was 505 ms
Day 22	16 days after cessation of all QTc-prolonging drugs; QTc interval was 476 ms

Case presentation

A 66-year-old female with a medical history of type 2 diabetes mellitus, hypercholesterolaemia, mild renal impairment, and cardiac catheterization in 2012 for symptoms of angina (no significant coronary artery disease) presented to the emergency department with symptoms of fatigue and diarrhoea for the last 10 days. She reported coughing in the last few days and had visited a sister-in-law positive for COVID-19. She used gliclazide 60 mg once daily, lisinopril 10 mg once daily, and metformin 200 mg twice daily, and had been prescribed ciprofloxacin 500 mg twice daily the day before by her general practitioner to treat her symptoms.

On arrival to the emergency department, body temperature was 38°C, blood pressure 98/69 mmHg, with a heart rate of 92 b.p.m. Her oxygen saturation was 94% with 12 L of O_2 per minute through a non-rebreather mask. Pulmonary examination revealed tachypnoea and bilateral coarse crackles upon auscultation. Her heart rhythm was regular with normal first and second heart sounds without murmurs. Findings on chest radiography showed a multifocal, bilateral, and peripheral ground-glass pattern. Blood tests demonstrated increased C-reactive protein levels of 113 mg/L (reference value <10 mg/L), impaired renal function with creatinine levels of 107 µmol/L (reference value 50–90 µmol/L) and CKD-EPI of 47 mL/min/1.73 m^2 (reference value >90 mL/min/1.73 m^2), with normal levels of potassium and sodium.

The patient was admitted to the internal medicine ward. Ceftriaxone 2 g once daily was administered intravenously, while ciprofloxaxin was discontinued. COVID-19 was confirmed by a nasopharyngeal swab testing positive for SARS-CoV-2 using real-time reverse transcription–polymerase chain reaction (RT–PCR) assay. Several hours after the patient's admission, her clinical condition worsened. Antiviral therapy with chloroquine was initiated according to recent guidelines, with a loading dose of 600 mg orally and a maintenance dose of 300 mg twice a day for a total of 5–7 days. The 12-lead ECG at baseline showed a QTc interval of 429 ms.

In the days thereafter, her condition progressively deteriorated, with oxygen saturation <90% and increased respiratory effort. She was then transferred to the ICU for mechanical ventilation on the third day of admission. Chest CT on the fifth day of admission showed widespread bilateral ground-glass opacities and consolidations in the lower lobes, but also bilateral segmental and subsegmental pulmonary embolisms. Because of QTc prolongation (QTc interval 482 ms), treatment with chloroquine was discontinued on the fifth day of admission. Unfortunately, treatment with erythromycin 250 mg twice daily started on the sixth day of admission to improve gastrointestinal motility. At the start of erythromycin treatment the QTc interval was 453 ms. On the seventh day of admission, the patient was resuscitated because of TdP (*Figure 1C*). Erythromycin was discontinued and concomitant treatment with 2 g of intravenous magnesium was initiated.

Retrospective evaluation of the multiple-lead telemetric monitor showed progressive QTc interval prolongation with a duration up to 550 ms and development of large U waves (*Figure 1B*). Bradycardia and late coupled ventricular ectopy in bigeminy resulted in short–long–short interval-initiated TdP (*Figure 1C*). Reversible causes of QT interval prolongation were investigated. Blood tests showed restored renal function and normal levels of electrolytes, with the exception of phosphate (0.88 mmol/L; reference value 0.90–1.50 mmol/L), which was corrected with oral glycophosphate. Acute ischaemia was excluded, with no significant rise or fall in high sensitivity troponin T. Transthoracic echocardiogram showed normal dimensions of the ventricles with normal systolic function (left ventricular ejection fraction ±50%). The patient's past medical history made significant coronary artery disease as a contributing factor unlikely. Earlier ECG registrations and treadmill testing from 2012 up to 2017 showed a normal QT interval, making underlying congenital long QT unlikely. Continued close monitoring of the QT interval showed no recurrent episodes of TdP. On the eighth day of admission, the QTc interval was 507 ms (*Figure 2A*) and, on the 16th day of admission, the QTc interval was almost completely normal (*Figure 2B*). The patient recovered gradually and was tested negative for COVID-19 on the 52nd day of admission. She was discharged from the hospital on the 62nd day of admission to a rehabilitation centre. After full recovery, appropriate long QT analysis will be conducted.

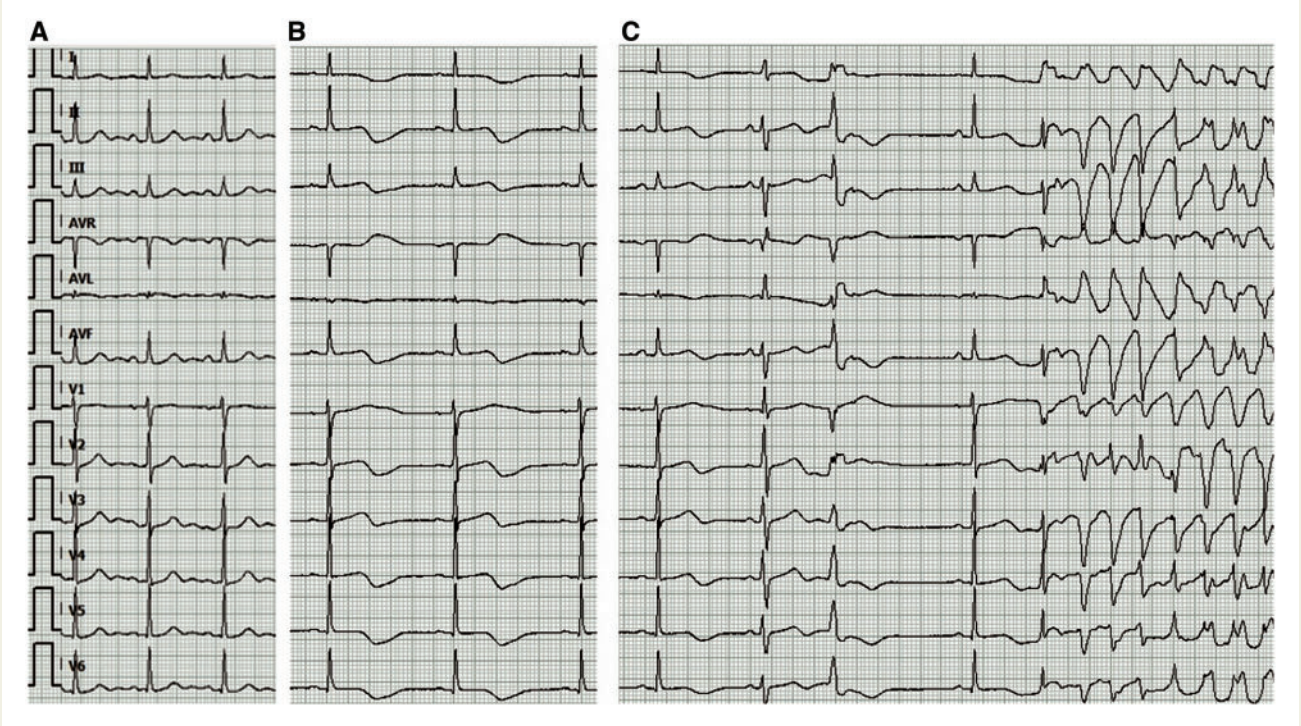

Figure 1 (*A*) Baseline ECG 1 day after cessation of chloroquine, before starting erythromycin (QTc 453 ms). (*B*) Two days after cessation of chloroquine, second day of erythromycin; severely prolonged QT interval and large U waves can be observed (QTc 522 ms). (*C*) Hours later, demonstrating the onset of 'Torsade de Pointes' (TdP); severely prolonged QT interval promoting early afterdepolarization-related late coupled ventricular ectopy in bigeminy. The short-long-short R-R interval in the last few complexes initiates TdP (QTc 547 ms). Paper speed 25 mm/s

Discussion

Extensive efforts in finding an effective treatment for symptomatic COVID-19 patients have led to repositioning of old drugs for use as antiviral treatment. Early non-peer-reviewed clinical trials have led to worldwide prescription of the antimalarials chloroquine and hydroxychloroquine. Subsequent observational studies in China showed no clinical benefit from hydroxychloroquine use in COVID-19 patients.[4] A phase IIb clinical trial in Brazil with chloroquine in COVID-19 patients was discontinued because of excessive mortality.[5] Even more recently, a multinational registry associating chloroquine with increased in-hospital mortality was published,[3] but has been retracted because of concern regarding the data. This makes interpretation of the benefit of chloroquine treatment difficult, but the high-risk adverse effects should be weighed against the moderate and uncertain benefit of these antimalarials.

This case is a unique presentation of a critically ill COVID-19 patient who developed TdP despite cessation of chloroquine treatment but after the start of erythromycin. The half-life of erythromycin ranges between 2.4 and 3.1 h. Previous 5-day chloroquine treatment had been discontinued 2 days prior to the event. However, chloroquine has a half-life ranging from 20 days up to 60 days.[6] The combination of chloroquine, in the setting of its long half-life, and erythromycin (and possibly a reduced repolarization reserve in our patient) resulted in severe acquired QT prolongation promoting early afterdepolarizations (EADs). These EADs can cause late coupled ventricular ectopic activity and subsequent initiation of TdP.

The risk for TdP increases markedly when the QTc interval exceeds 500 ms.[7] A prolonged QTc interval can be the result of extrinsic causes or genetic predisposition. Risk factors for acquired QTc interval prolongation include electrolyte disturbances, structural heart disease, ischaemia, bradycardia, female sex, advanced age, history of QTc prolongation, genetic polymorphisms, and drugs. Hospitalized patients may be at greater risk for drug-induced QTc prolongation and TdP due to the presence of these risk factors.

The antimalarial drugs chloroquine and hydroxychloroquine are widely used in the long-term treatment of systemic lupus erythematosus and rheumatoid arthritis.[8] They have QT-prolonging effects by blocking the potassium channel IKr (hERG/Kv11.1).[9] Chloroquine and hydroxychloroquine have a long half-life, ranging from 20 to 60 days, and a tendency to accumulate in metabolically active tissues at higher levels compared with the plasma concentration, which are prerequisite for delayed toxic effects.[6] Reports of long QT are mostly seen with chronic use, concomitant with other risk factors (e.g. use of multiple concomitant QT-prolonging medications, metabolic derangements, renal failure, or in the setting of an acute overdose).[10] Recently

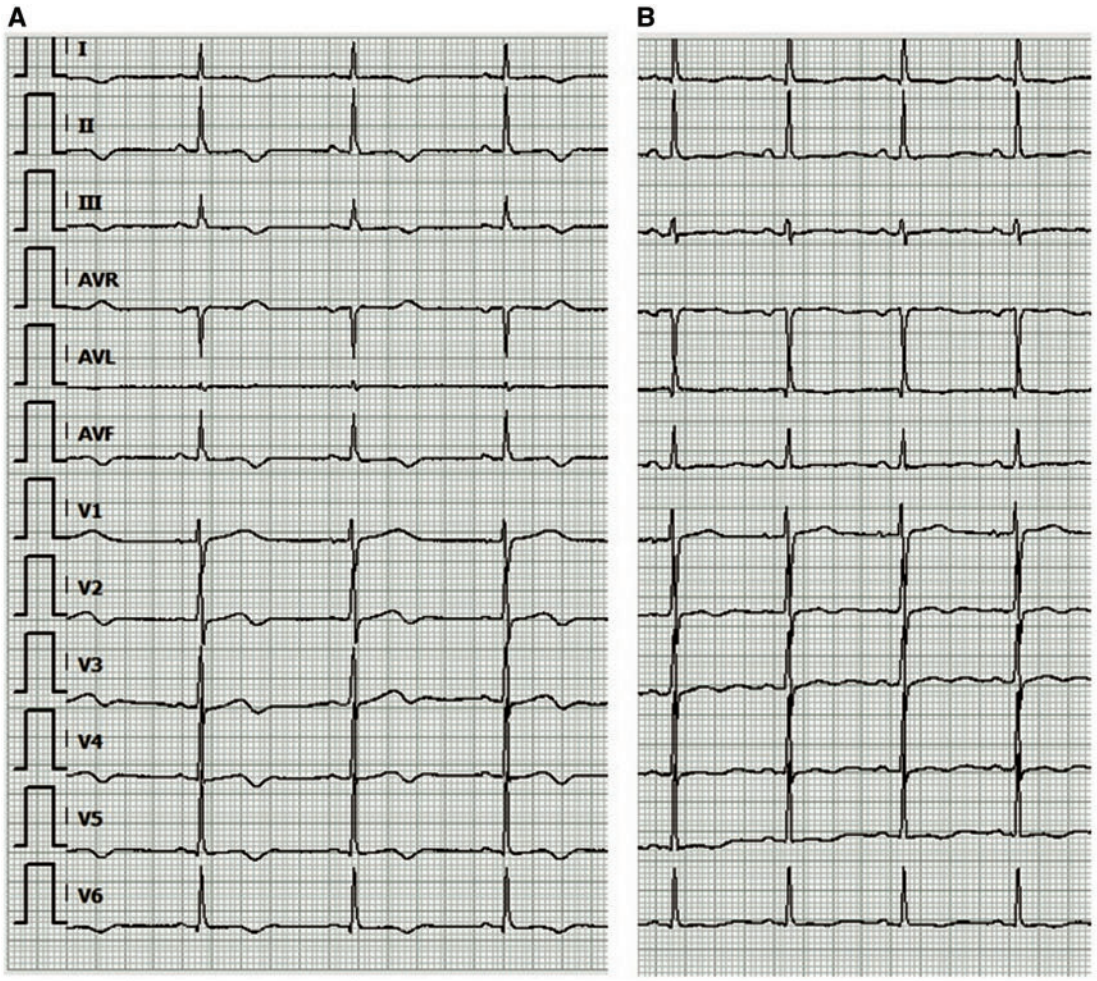

Figure 2 Serial ECG registration after cessation of QT-prolonging drugs. (*A*) Day 8 (QTc 505 ms). (*B*) Day 16 almost completely restored (QTc 476 ms). Paper speed 25 mm/s.

published clinical studies in the Netherlands demonstrated a mean QTc interval prolongation of 35 ms in a COVID-19 patient treated with chloroquine.[11] This case illustrates that even for shorter periods of time, chloroquine can become a potent risk factor for QTc interval prolongation in the critically ill COVID-19 patient, especially when other potentially QT-prolonging drugs are introduced.

Conclusion

Despite early reports, more recent studies have shown that there is increased mortality and adverse effects in the critically ill COVID-19 patient treated with chloroquine. Chloroquine can cause significant QT interval prolongation, increasing the risk of life-threatening cardiac arrhythmias, especially TdP. The long half-life of this drug warrants long-term ECG monitoring, even after cessation of these drugs. We recommend ECG monitoring in cases where other potentially QT-prolonging drugs are introduced.

Lead author biography

Edimir Semedo is a third-year resident at Department of Cardiology, Thoraxcentrum Twente, the Netherlands. His fields of interest are electrophysiology and critical care cardiology.

Supplementary material

Supplementary material is available at European Heart Journal – Case Reports online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent : The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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