WHAT IS KNOWN AND OBJECTIVE

Life-threatening arrhythmias, including torsades de pointes (TdP) and ventricular fibrillation, may be induced by corrected QT (QTc) prolongation. Here, we report on two cases in which patients with novel coronavirus disease (COVID-19) experienced QTc prolongation during antiviral treatment at our institution. The relationship between QTc interval prolongation and severe acute respiratory syndrome coronavirus 2 (SAR-CoV-2) infections remains uncertain. However, acquired long QT syndrome secondary to drug-induced QT prolongation and TdP has been reported for several antiviral drugs.

CASE DESCRIPTION

2.1 | Case 1

A 56-year-old woman with diarrhoea and fever for 4 days was confirmed to have COVID-19 pneumonia via chest computed tomography scans performed on 1 February 2020. She denied a history of chronic illness and related medications. The patient was treated with oral lopinavir/ritonavir 400/100 mg twice daily from February 3 to February 13, oral arbidol 0.2 g three times daily from February 3 to February 19, oral pantoprazole 40 mg daily from February 6 to February 19, methylprednisolone 40 mg intravenously from February 9-February 16 and...
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chloroquine 0.25 g twice daily from February 11 to February 21. On February 12, an atrial rate of 72 bpm and a calculated QTc interval of 482 ms were recorded (Figure 1). On that day, her plasma K⁺ was 3.6 mmol/L, Na⁺ was 139 mmol/L, total calcium was 1.91 mmol/L, and creatine phosphokinase was 59 U/L; no other cardiac biomarkers were measured. After lopinavir/ritonavir withdrawal, the QTc interval...
decreased to 451 ms and 410 ms on February 13 and February 16, respectively. The patient was administered potassium chloride at a dose of 1 g three times daily from February 13 to February 16; on February 17, her plasma K⁺ was 5.0 mmol/L, Na⁺ was 146 mmol/L, and total calcium was 2.05 mmol/L. She was discharged from the hospital in good general condition (Figure 3, Upper).

2.2 | Case 2

A 56-year-old woman presenting with fever for one day was confirmed to have COVID-19 pneumonia via throat swab samples on 2 February 2020. She denied a history of chronic illness and related medication. The patient was treated with oral lopinavir/ritonavir 400/100 mg twice daily from February 5 to February 13, oral arbidol 0.2 g three times daily from February 5 to February 19, oral pantoprazole 40 mg daily from February 8 to February 22 and oral chloroquine 0.25 g twice daily from February 12 to February 22. On February 10, her plasma K⁺ was 3.8 mmol/L, Na⁺ was 144 mmol/L, total calcium was 2.15 mmol/L and creatine phosphokinase was 44 U/L; no other cardiac biomarkers were measured. On February 12, an atrial rate of 78 bpm and a calculated QTc interval of 467 ms were recorded (Figure 2). On February 15, 2 days after the withdrawal of lopinavir/ritonavir, the QTc interval decreased to 422 ms. The patient was administered oral potassium chloride 1 g three times daily from February 13 to February 17. On February 17, her plasma K⁺ was 4.7 mmol/L, Na⁺ was 146 mmol/L, and total calcium was 2.22 mmol/L. She was discharged from the hospital in good condition. An electrocardiogram (ECG) performed on 19 August 2018 did not show conduction disorders or QT prolongation (Figure 3, Lower).

According to the American Heart Association/ American College of Cardiology Foundation Scientific Statement, the QTc values for healthy males and females are 470 ms and 480 ms, respectively. For both sexes, a QTc interval of 500 ms is considered highly abnormal. On the day before the last dose of lopinavir/ritonavir, the QTc intervals for Cases 1 and 2 reached 482 ms and 467 ms, respectively. The side effects were mild; however, fatal outcomes were possible without early identification of the causes of potentially reversible QT prolongation. Thus, we attempted to detect the possible causes QTc prolongation, considered the possibility of acquired long QT syndrome and weighed the risk of QTc prolongation against the expected benefits of antiviral treatment in COVID-19 patients.

Independent risk factors that can predispose a person to QT prolongation, and TdP include female sex, age (over 65 years), bradycardia, hypokalaemia, hypomagnesaemia, underlying heart disease, renal and hepatic dysfunction, drug-drug interactions, high concentrations of one or more QTc-prolonging drugs and genetic predisposition. During hospitalization, no other evidence of heart disease or renal and hepatic dysfunction was found in our patients. Women account for approximately 70% of cases of drug-induced QT prolongation and TdP; both patients were female. Given their history of medication use, a drug-induced acquired long QT interval syndrome was suspected. Anson et al reported in vitro data that suggested lopinavir causes dose-related blockade of human ether-à-go-go-related gene (hERG) potassium channels and rapidly activating rectifier K⁺ current (IKr). Similar results have been found for nelfinavir, ritonavir and aquinavir therapies. Another drug administered to our patients, chloroquine, can potentially prolong QTc intervals. Chloroquine, which has an elimination half-life of 2.5 days to 10 days and requires several oral doses before reaching steady state, was administered one or two days before the detection of QTc prolongation; this suggests that chloroquine had a limited role in the patients’ QTc prolongation. However, it cannot be denied that administration of multiple QTc-prolonging drugs increases the risk of QTc prolongation. In addition, the extended use of proton-pump inhibitors (PPIs) has been associated with hypomagnesaemia and subsequent QT interval prolongation. We could not monitor Mg plasma levels in our patients, but their short courses of PPIs and the reduction of QTc intervals while continuing PPI therapy made it unlikely that pantoprazole played a role in the prolongation of their QTc intervals.

Other electrolyte disturbances, particularly hypokalaemia, can induce QTc prolongation. Both patients’ plasma K⁺ and Na⁺ levels were within normal range, and Case 1 had a slightly low calcium level (1.91 mmol/L) when QTc prolongation was recorded. Several studies have analysed whether hypocalcaemia is an independent risk factor for QTc interval prolongation; however, their results have been inconsistent. In one study, calcium levels below 1.69 mmol/L were associated with prolongation of the QTc interval by 20.4 ms.11

Drug-drug interaction must also be considered. Lopinavir/ritonavir is a potent inhibitor of CYP3A4; therefore, lopinavir/ritonavir may have potentially enhanced the pharmacological and toxicological effects of arbidol, which is predominantly metabolized by CYP3A4. These results indicated possible drug interactions between arbidol and lopinavir/ritonavir in our patients, thus increasing the possibility of QTc interval prolongation.

As we know, some viruses (eg human immunodeficiency virus, hepatitis C virus and West Nile virus) are associated with QTc interval prolongation. However, the relationship between QTc prolongation and SAR-CoV-2 infection remains uncertain. In the first reported case on the pathological findings of COVID-19, there were a few interstitial mononuclear inflammatory infiltrates but no other substantial damage in heart tissues. Histologic studies were not performed; however, based on the patients’ relatively young ages, their absence of underlying heart diseases, and reductions in their QTc intervals after withdrawal of lopinavir/ritonavir, we believe that gender, drug-drug interaction and the administration of lopinavir/ritonavir may have contributed to QTc prolongation.

3 | WHAT IS NEW AND CONCLUSION

Drugs currently used in COVID-19 patients, including HIV protease inhibitors and antimalarials such as chloroquine, have been associated with QTc prolongation. The co-administration of QT-prolonging medications with drugs that interfere with their metabolism must be
considered. Moreover, ECGs should be performed and QTc intervals should be carefully analysed at baseline and during therapy to identify individuals at high risk of arrhythmias.

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CONFLICT OF INTEREST
The authors declare no conflicts of interest.

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