Blood Purification

Case Report

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Sudden Cardiac Death in Haemodialysis Patients under Hydroxychloroquine Treatment for COVID-19: A Report of Two Cases

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Keywords
Coronavirus disease-19 · End-stage renal disease · Haemodialysis · Hydroxychloroquine · Sudden death

Abstract
Hydroxychloroquine (HQ) has been used for the treatment of novel coronavirus disease (COVID-19) even though there is no clear evidence for its effectiveness yet. In contrary, HQ has major side effects like QTc prolongation and subsequent development of ventricular arrhythmias. Such side effects may possess additional risks on end-stage renal disease (ESRD) patients who have higher cardiovascular risks than general population. We herein present 2 cases of sudden cardiac death in 2 ESRD patients with COVID-19 for whom a treatment regimen including HQ was preferred. Both patients were clinically stable at the time of arrest. Death could not be attributed to worsening of the COVID-19 since the patients' clinical picture and laboratory values were improving. The cardiac events coincided with the end of routine haemodialysis sessions of both patients. Electrocardiography controls upon admission and on the 24 and 48 h of treatment showed normal QTc intervals. Potential risks contributing to sudden cardiac death during HQ treatment of ESRD patients are discussed.

Introduction

Hydroxychloroquine (HQ) has been a part of many guidelines to treat a novel coronavirus disease (COVID-19) worldwide although its effectiveness is still questionable [1], and its side effects are generally underestimated. The most worrisome side effect of HQ is ventricular arrhythmia. Prolonged QTc intervals may give a clue, however, using the drug may not be absolutely safe even if the QTc interval is within the normal range [2].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-clearing effect of HQ is better when it is given in doses higher than 400 mg [3]. However, its arrhythmogenic potential may be increasing in such high doses. For increased effectiveness of HQ in decreasing the viral load, guidelines recommend an 800 mg loading dose, followed by 400 mg for daily maintenance [4]. Azithromycin is given in combination with HQ since it intensifies its effectiveness with antiviral and immunemodulatory properties [5]. Physicians should monitor QTc interval upon admission and throughout the treatment.

In this study, we report 2 end-stage renal disease (ESRD) patients who experienced sudden cardiac death while on HQ treatment for COVID-19. We prescribed

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reduced dose HQ (100 mg of maintenance dose after 400 mg of loading dose) and azithromycin combination for both patients.

Case Report/Case Presentation

Patient 1

A 73-year-old male ESRD patient was referred to the emergency department with symptoms of general malaise, cough and dyspnoea. The patient had basal fine crackles on auscultation. His lymphocyte count was 1×10^9/L, and C-reactive protein (CRP) and lactate dehydrogenase levels on admission were 157 mg/dL and 421 IU/L, respectively. Chest computed tomography revealed bilateral ground-glass opacities. Real-time polymerase chain reaction from nasopharyngeal swab for SARS-CoV-2 was positive. Patient was admitted and treated with a treatment scheme including HQ, azithromycin and low-molecular-weight heparin. His QTc interval was normal upon admission and also on the 24 and 48 h of the treatment. Haemodialysis (HD) sessions were resumed 3 times weekly. Potassium levels ranged between 3.4 and 3.8 mEq/L during hospital stay. His COVID-19 symptoms were improving on the 3rd day of the treatment, when he had cardiac arrest at the end of a routine haemodialysis session. There was no intradialytic hypotension, and ultrafiltration did not exceed 2,000 mL during a 4-h haemodialysis session. The patient did not need any respiratory support while his CRP levels and other inflammatory markers were decreasing. Troponin and creatine kinase-MB (CK-MB) levels were also normal at the time of death.

Patient 2

An 80-year-old female ESRD patient was investigated for nausea and vomiting. She was tachypneic at rest, and her physical examination was unremarkable except for mild pretibial oedema. Laboratory tests revealed a lymphocyte count of 0.9×10^9/L, CRP level of 352 mg/dL and a LDH level of 945 IU/L. As D-dimer level was also as high as 11 mg/L, a chest computed tomography scan with contrast was performed. There were no pulmonary emboli, however, lung scan showed bilateral ground-glass opacities with consolidation. Nasopharyngeal swab for SARS-CoV-2 real-time polymerase chain reaction was positive. The patient was admitted to the COVID ward. A combination of HQ and azithromycin was prescribed in addition to a prophylactic dose of low-molecular-weight heparin. The patient did not have long QTc upon admission, and ECG controls on the 24 and 48 h were also normal. Haemodialysis sessions were planned in our isolated HD facility. The patient's clinical condition was stable when she experienced a cardiac arrest at the end of a routine haemodialysis session on the 4th day of admission. She needed intermittent nasal oxygen support during her hospital stay, but her respiratory symptoms did not become worse during the inpatient follow-up. The high D-dimer level on admission further increased to 16 mg/L on the 3rd day, but the patient's clinical picture did not seem to deteriorate. She had mild interdialytic high potassium levels, reaching 5.8 mEq/L. The patient did not have hypotension during a 3-h HD session. Ultrafiltration was kept around 2,000 mL. Blood troponin and CK-MB levels at the time of death were both normal.

Discussion/Conclusion

The most probable cause of sudden death in these presented patients is cardiac arrhythmia. Hydroxychloroquine has an arrhythmogenic potential to cause ventricular arrhythmias, including torsades de pointes [6]. The potassium-lowering effect of HQ may increase its arrhythmogenic potential [7]. Relatively lower potassium levels below 4 mEq/L in Patient #1 and interdialytic hyperkalaemia in Patient #2 resulting in higher potassium shifts during haemodialysis session might have increased the arrhythmogenic potential of HQ. Such potassium shifts should be avoided, as they increase the arrhythmia risk even in normal haemodialysis patients [8]. One may also blame the combination of azithromycin and HQ, since both are QT-prolonging agents. However, QTc intervals upon admission, on the 24 and 48 h of the treatment, were all normal in both patients. Hence, continuing the treatment was thought to be safe. Azithromycin was used in our cases because of its antiviral and immune-modulatory properties [9]. We would like to stress out that, since they have cardiac side effects, macrolides and quinolones should not be preferred if an anti-bacterial coverage is needed in the course of COVID-19 treatment. Beta-lactam antibiotics or cephalosporins are better 1st-line options for such indication [10]. Regarding other sudden cardiac death risks for HD patients [11], presented patients did not have prominent hypervolemia, and ultrafiltration was neither excessive nor rapid during the HD sessions. Myocardial infarction was also ruled out since both patients had normal troponin and CK-MB levels at the time of cardiac arrest. The advanced age of the presented patients might have also contributed to the cardiac event. Death was not attributed to worsening of COVID-19 since both patients were clinically stable in the ward and their cardiac arrest occurred just at the end of the haemodialysis sessions. Our experience in these 2 cases rose major safety concerns for using HQ in ESRD patients.

We believe that, especially for chronic haemodialysis patients older than 65 years, HQ should be used with caution even if QTc intervals are calculated to be normal. Some recommendations to mitigate HQ-related cardiac risks in ESRD patients are as follows:

- Keep serum potassium level above 4 mEq/L.
- Keep serum magnesium level above 2 mEq/L.
- Avoid interdialytic hyperkalaemia.
- Use dialysates with potassium concentrations over 2 mEq/L and calcium concentrations over 1.25 mmol/L.
- Do not decrease the number of or shorten the length of the haemodialysis sessions. This will help to avoid interdialytic hyperkalaemia and hypervolemia.

Statement of Ethics

Written informed consents for publication of the data and images have been taken from patients and their relatives. Information revealing the patients' identities is avoided.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Ahmet Murt did the literature search, wrote the main text and submitted the work. Mevlut Tamer Dincer helped in writing of the text. Cebrail Karaca controlled data from the patient files.

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