Torsade de pointes caused by hydroxychloroquine use in a patient with a severe form of COVID-19

Y Zarrouki, MD; OrcID 0000-0001-5243-2735; **H Rebahi,** MD; **M Rhezali,** MD; **F Douirek,** MD; **A Ziad,** MD; **M A Samkaoui,** MD

Department of Anaesthesiology and Intensive Care, Faculty of Medicine and Pharmacy, Cadi Ayyad University, Marrakesh, Morocco

Corresponding author: *Z Youssef (zarroukiyoussef@gmail.com)*

We report the case of a previously healthy patient who was severely affected by COVID-19 and developed *torsade de pointes* after hydroxychloroquine-azithromycin administration. Critically ill COVID-19 patients have multiple abnormalities that lead to an unsteady state in heart electricity, and can potentiate hydroxychloroquine cardiotoxicity. In light of this clinical observation, and until the efficacy of this association is proven, we plead against its use in critically ill COVID-19 patients.

South Afr J Crit Care 2020;36(1):12-13. https://doi.org/10.7196/SAJCC.2020.v36i1.449

The COVID-19 pandemic has led to large-scale off-label prescription of hydroxychloroquine (HCQ). Health authorities argue for its efficacy by analogy with its effective use in autoimmune disorders and Middle East respiratory syndrome (MERS).[1] In fact, this antimalarial drug, according to solid evidence, possesses anti-inflammatory, immunomodulatory and antiviral properties.[2] However, HCQ has raised many safety issues, mainly when combined with azithromycin (AZI) in severe forms of COVID-19-related acute respiratory distress syndrome. This paper highlights arrhythmia complications owing to HCQ in a critically ill patient, and discusses the potential underlying mechanisms of the drug. A 53-year-old woman with no significant past medical history was admitted to the intensive care unit for severe COVID-19-related acute respiratory distress syndrome (C-ARDS). An electrocardiogram was performed on admission, and showed a normal QTc, so she received a combination of 600 mg HCQ three times a day and 250 mg AZI once daily. On day 4, her clinical course was marked by the onset of arrhythmia characterised by premature ventricular complex (Fig. 1) repeated occasionally in bigeminy patterns (Fig. 2). Blood potassium and magnesium levels were normal. Thirteen minutes later, the electrical abnormalities were followed by a *torsade de pointes* occurrence with twisting of the QRS complexes around the isoelectric line (Fig. 3). An intravenous bolus associated with continuous perfusion of magnesium sulfate allowed prompt return and maintenance of normal rhythm. Additionally, combination HCQ-AZI was ceased. The outcome was favourable, with absence of arrhythmia recurrence, mechanical ventilation weaning and reverse transcription-polymerase chain reaction negativation, and the patient was discharged at day 27 and did not require further treatment for her arrhythmia.

HCQ is a well-known antimalarial drug and has been indicated over the last decades for lupus and rheumatoid arthritis, with a large safety margin. Extrapolation of this utilisation in COVID-19 remains controversial, despite its adoption in many countries as first-line therapy.[3,4] Indeed, many concerns have been raised in severely affected patients, and recently the US Food and Drug Administration cautioned against its use for COVID-19 outside of the hospital setting owing to the risk of heart rhythm problems. The occurrence of *torsade de pointes* in this SARS-CoV-2-infected patient suggests intricate mechanisms that could possibly potentiate the action of HCQ-AZI therapy: (*i*) direct viral

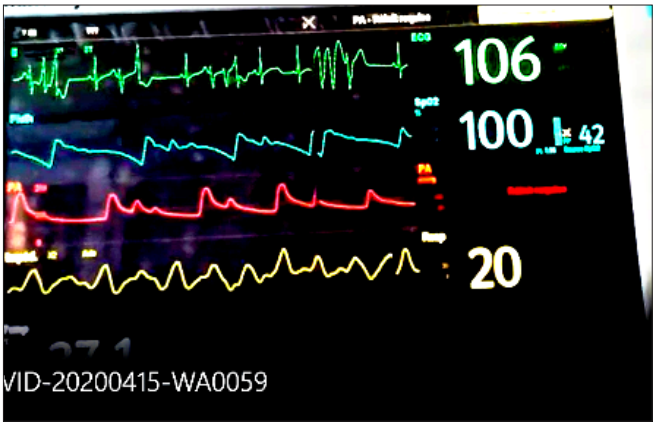

Fig. 1. Arrhythmia characterised by premature ventricular complex.

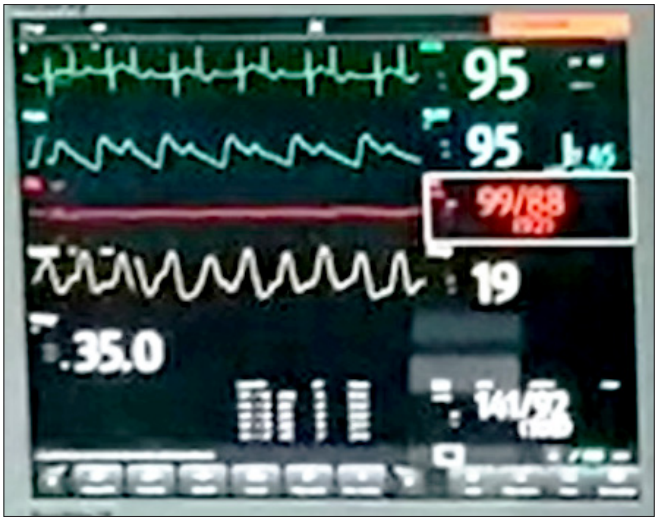

Fig. 2. Arrhythmia characterised by bigeminy patterns.

effects on myocardium and conduction system, causing an unsteady state in myocardial electricity;[5] (*ii*) C-ARDS-induced hypoxia/hypercapnia leading to a pro-arrhythmogenic state; or (*iii*) a dysregulated immune response to the SARS-CoV-2 infection leading to cytokine storm-related cardiac cell damage.[6] Furthermore, many other factors, such as acidosis,

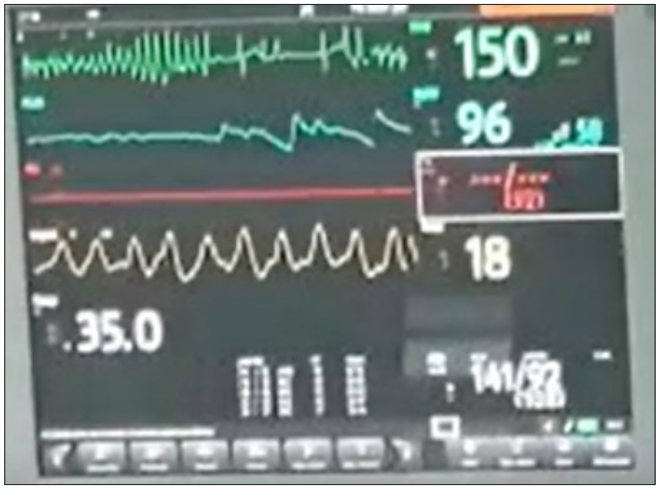

Fig. 3. Torsade de pointes *that regressed after an intravenous bolus of magnesium sulphate.*

hyperthermia and the use of sympathomimetic drugs can precipitate the occurrence of cardiac arrhythmia.[7]

In light of the above considerations, and until the efficacy of HCQ-AZI association is proven,[3,4] we plead against its use in critically ill COVID-19 patients.

Declaration. None.

Acknowledgements. None.

Author contributions. All authors contributed to care and redaction.

Funding. None.

Conflicts of interest. None.

1. Dyall J, Coleman CM, Hart BJ, et al. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. Antimicrob Agents Chemother 2014;58(8):4885-4893. https://doi.org/10.1128/AAC.03036-14
2. Changfeng Hu, Lu Lu, Jie-Ping Wan, Chengping Wen. The pharmacological mechanisms and therapeutic activities of hydroxychloroquine in rheumatic and related diseases. Curr Med Chem 2017;24(20):2241-2249. https://doi.org/10.2174/0929867324666170316115938
3. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalised patients with COVID-19. New Engl J Med 2020;382:2411-2418. https://doi.org/10.1056/nejmoa2012410
4. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA 2020;323(24):2493-2502. https://doi.org/10.1001%2Fjama.2020.863
5. Kochi AN, Tagliari AP, Forleo GB, Fassini GM, Tondo C. Cardiac and arrhythmic complications in patients with COVID-19. J Cardiovasc Electrophysiol 2020;31(5):1003-1008. https://doi.org/10.1111/jce.14479
6. Lazzerini PE, Boutjdir M, Leopoldo Capecchi PL. COVID-19, arrhythmic risk and inflammation: Mind the gap! Circulation 2020;(epub 14 April 2020). https://www.researchgate.net/deref/http%3A%2F%2Fdx.doi.org%2F10.1161%2FCIRCULATIONAHA.120.047293
7. Heinz G. Arrhythmias in the ICU: What do we know? Am J Respir Crit Care Med 2008;178(1):1-2. https://doi.org/10.1164/rccm.200804-554ed

Accepted 28 May 2020.