Chloroquine or hydroxychloroquine for COVID-19: why might they be hazardous?

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The 4-aminoquinoline antimalarials chloroquine and hydroxychloroquine have been promoted and sometimes used in the treatment of COVID-19, alone or combined with azithromycin, based on their immunomodulatory and antiviral properties, despite an absence of methodologically appropriate proof of their efficacy. The global community awaits the results of ongoing, well powered randomised controlled trials showing the effects of chloroquine and hydroxychloroquine on COVID-19 clinical outcomes. These drugs, however, might be associated with cardiac toxicity. Macrolides[1] and 4-aminoquinolines[2] prolong ventricular repolarisation, as evidenced by QT interval prolongation corrected for heart rate (QTc) on the electrocardiogram. QTc prolongation can be associated with a specific ventricular arrhythmia called torsade de pointes, which, although often self-terminating, can degenerate into ventricular tachycardia or fibrillation, leading to death. Torsade de pointes is a rare event, with an estimated annual crude incidence of 3·2 per million population; the incidence is almost doubled in women compared with men and increases with age.[3] Drug-induced torsade de pointes mostly occurs in the presence of several risk factors, including high drug concentration, simultaneous exposure to multiple QTc-prolonging drugs, coronary heart disease, heart failure, hypokalaemia, bradycardia, or congenital long-QT syndrome, among others.[4]

In *The Lancet*, Mandeep Mehra and colleagues[5] report the largest observational study published to date on the effects of chloroquine or hydroxychloroquine, with or without a macrolide, in 96 032 hospitalised patients (mean age 53·8 years, 46·3% women) who tested positive for severe acute respiratory syndrome coronavirus 2. Verified data from an international registry comprising 671 hospitals in six continents were used to compare patients with COVID-19 who received chloroquine (n=1868), hydroxychloroquine (n=3016), chloroquine with a macrolide (n=3783), or hydroxychloroquine with a macrolide (n=6221) within 48 h of COVID-19 diagnosis, with 81 144 controls who did not receive these drugs. The primary outcome was in-hospital mortality and the occurrence of de-novo non-sustained or sustained ventricular tachycardia or ventricular fibrillation was also analysed. A Cox proportional hazard model accounting for many confounding variables, including age, sex, ethnicity, comorbidities, other medications, and COVID-19 severity, showed a significant increase in the risk of in-hospital mortality with the four treatment regimens compared with the control group (hazard ratios [HRs] of 1·335 [95% CI 1·223–1·457] to 1·447 [1·368–1·531]). Analyses using propensity score matching by treatment group supported this result. The increased risk of in-hospital mortality was similar in men (1·293 [1·178–1·420] to 1·408 [1·309–1·513]) and women (1·338 [1·169–1·531] to 1·494 [1·334–1·672]). The incidence of repetitive ventricular arrhythmias ranged from 4·3% to 8·1% in patients treated with a 4-aminoquinoline, compared with 0·3% in the control group (p<0·0001).

Despite limitations inherent to the observational nature of this study, Mehra and colleagues should be commended for providing results from a well designed and controlled study of the effects of chloroquine or hydroxychloroquine, with or without a macrolide, in a very large sample of hospitalised patients with COVID-19. Their results indicate an absence of benefit of 4-aminoquinoline-based treatments in this population and suggest that they could even be harmful. It is tempting to attribute the increased risk of

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in-hospital deaths to the higher observed incidence of drug-induced ventricular arrhythmias, given that these drugs are known to prolong QTc and provoke torsade de pointes. However, the relationship between death and ventricular tachycardia was not studied and causes of deaths (ie, arrhythmic *vs* non-arrhythmic) were not adjudicated. Although not all ventricular arrhythmias might have been detected, the number of deaths in the treatment groups was much greater than the number of patients who had ventricular arrhythmias. The risk of death associated with 4-aminoquinolines alone or combined with a macrolide was similar, whereas it would be expected that the combination of two QTc-prolonging drugs would increase their proarrhythmic potential.[6] The HRs for death were similar in men and women, whereas women have a higher sensitivity to drug-induced QTc prolongation[7] and a higher risk of drug-induced torsade de pointes[3] than men. The study therefore does not suggest that the increased risk of death with 4-aminoquinolines was due to a proarrhythmic mechanism. Another hypothesis to explain the increased risk of death with 4-aminoquinolines is that their antiviral and immunomodulatory properties could worsen COVID-19 severity in some patients. Nevertheless, the increased incidence of ventricular arrhythmias is intriguing. Chloroquine,[8] hydroxychloroquine,[9] and azithromycin[10] have sodium channel blocking properties that might contribute to proarrhythmia[11] and heart failure in the context of myocardial injury and hypoxia present in COVID-19.[12] This hypothesis remains to be tested.

The findings from Mehra and colleagues' study add to preliminary reports suggesting that regimens of chloroquine or hydroxychloroquine, alone or with azithromycin, are not useful and could be harmful in hospitalised patients with COVID-19.

We declare no competing interests.

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1 Mason JW. Antimicrobials and QT prolongation. *J Antimicrob Chemother* 2017; **72:** 1272–74.
2 White NJ. Cardiotoxicity of antimalarial drugs. *Lancet Infect Dis* 2007; **7:** 549–58.
3 Sarganas G, Garbe E, Klimpel A, Hering RC, Bronder E, Haverkamp W. Epidemiology of symptomatic drug-induced long QT syndrome and torsade de pointes in Germany. *Europace* 2014; **16:** 101–08.
4 Vlachos K, Georgopoulos S, Efremidis M, Sideris A, Letsas KP. An update on risk factors for drug-induced arrhythmias. *Expert Rev Clin Pharmacol* 2016; **9:** 117–27.
5 Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet* 2020; published online May 22. https://doi.org/10.1016/S0140-6736(20)31180-6.
6 Frommeyer G, Fischer C, Ellermann C, et al. Additive proarrhythmic effect of combined treatment with QT-prolonging agents. *Cardiovasc Toxicol* 2018; **18:** 84–90.
7 Darpo B, Karnad DR, Badilini F, et al. Are women more susceptible than men to drug-induced QT prolongation? Concentration-QTc modelling in a phase 1 study with oral rac-sotalol. *Br J Clin Pharmacol* 2014; **77:** 522–31.
8 Vicente J, Zusterzeel R, Johannesen L, et al. Assessment of multi-ion channel block in a phase I randomized study design: results of the CiPA phase I ECG biomarker validation study. *Clin Pharmacol Ther* 2019; **105:** 943–53.
9 Ten Broeke R, Mestrom E, Woo L, Kreeftenberg H. Early treatment with intravenous lipid emulsion in a potentially lethal hydroxychloroquine intoxication. *Neth J Med* 2016; **74:** 210–14.
10 Yang Z, Prinsen JK, Bersell KR, et al. Azithromycin causes a novel proarrhythmic syndrome. *Circ Arrhythm Electrophysiol* 2017; **10:** e003560.
11 Roden DM, Anderson ME. Proarrhythmia. *Handb Exp Pharmacol* 2006; **171:** 73–97.
12 Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020; published online March 27. DOI:10.1001/jamacardio.2020.1017.