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Retraction and republication: cardiac toxicity of hydroxychloroquine in COVID-19

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A recent *Lancet* Article by Mandeep Mehra and colleagues, which reported adverse events associated with hydroxychloroquine or chloroquine treatment in patients with COVID-19, has been retracted by three of the authors,[1] along with our linked Comment that provided a commentary on the Article and its findings,[2] because the veracity of the data underlying this observational study could not be assured by the study authors. Subsequently, an article that used data from the same Surgisphere database, and which was authored by some of the same individuals, was retracted from the *New England Journal of Medicine*. Nevertheless, the debate about hydroxychloroquine for COVID-19 continues. Here, we provide a discussion of what is currently known about its proven and potential harms.

Hydroxychloroquine is a 4-aminoquinoline that prolongs ventricular repolarisation, as evidenced by prolongation of the QT interval corrected for heart rate (QTc) on the electrocardiogram.[3] 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 rate of 3·2 per million population; the incidence is almost doubled in women compared with men and increases with age.[4] Drug-induced torsade de pointes mostly occurs by blockade of the cardiac rapid delayed rectifier channels 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.[5]

Severe proarrhythmic events with hydroxychloroquine were first reported in 1992 in the WHO pharmacovigilance database, VigiBase. Although under-reporting is expected in pharmacovigilance databases, the incidence of cardiac adverse events remained very low during decades of prescription, and previous reports were mainly concerned with overdose situations. We recently analysed cases of prolonged QT interval, cardiac conduction disorders, and torsade de pointes or ventricular tachycardia associated with hydroxychloroquine in VigiBase before the COVID-19 pandemic.[6] Using disproportionality analysis, we found a significant association between hydroxychloroquine and the reporting of prolonged QT interval or torsade de pointes or ventricular tachycardia versus the same adverse events with all other drugs in the database. However, the number of cases was small: 85 for prolonged QT interval and 83 for torsade de pointes or ventricular tachycardia. Seven (8%) of the 83 cases of torsade de pointes or ventricular tachycardia were fatal.

The risks of cardiac adverse events associated with hydroxychloroquine during the COVID-19 pandemic might increase for several reasons. Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have multiple risk factors for drug-induced proarrhythmia: hypokalaemia, in the 3·0–3·4 mmol/L range, is common; fever amplifies drug-induced blockade of cardiac rapid delayed rectifier channels; and an increase in interleukin-6 concentrations, as seen in SARS-CoV-2 infection, has been suggested as a mechanism of the QT prolongation associated with inflammation.[7] Also, high doses of hydroxychloroquine are often administered in COVID-19, many patients receive co-prescriptions with QT-prolonging drugs, including azithromycin,[7,8] and about 30% of patients with COVID-19 have myocardial injury.[9] These are risk factors for torsade de pointes or ventricular tachycardia.[5] QTc prolongation associated with hydroxychloroquine is amplified in patients with COVID-19 compared with non-COVID-19 patients, with 10–20% of patients with COVID-19 having QTc values of more than 500 ms.[10]

However, QTc prolongation is not the only mechanism that might be associated with an increased incidence of cardiac adverse events with hydroxychloroquine. QRS interval duration, a sodium-channel-dependent ventricular conduction parameter, is increased in patients with COVID-19 treated with hydroxychloroquine.[10] Sodium-channel blockade is amplified in depolarised cardiomyocytes, as is seen in myocardial ischaemia, and by rapid heart rates, two conditions that are associated with hypoxia and COVID-19.[9,11] This mechanism is known to be associated with re-entrant ventricular tachycardia, heart failure, and mortality.[5]

Recent randomised clinical trials have confirmed that hydroxychloroquine does not reduce mortality

of hospitalised patients with COVID-19.[12] The hydroxychloroquine arm of the RECOVERY trial, which used high doses of hydroxychloroquine, was stopped with preliminary results showing possible excess mortality with hydroxychloroquine (25·7% with hydroxychloroquine *vs* 23·5% with usual care; hazard ratio 1·11 [95% CI 0·98–1·26]; p=0·10).[13] The same trend was found in an observational study in which the adjusted odds ratio of cardiac arrest with hydroxychloroquine alone compared with no hydroxychloroquine was 1·91 (95% CI 0·96–3·81) and was significantly increased if hydroxychloroquine was combined with azithromycin (2·13 [1·12–4·05]);[8] however, mortality was not increased.

Several arguments support the hypothesis that hydroxychloroquine, in addition to having no beneficial effect in hospitalised patients with COVID-19, might have potentially fatal cardiac effects.

We declare no competing interests.

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