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Chloroquine and hydroxychloroquine for COVID-19: implications for cardiac safety

The recent COVID-19 pandemic highlights the need for rapid responses in developing treatment strategies for new and emerging diseases. The option to repurpose drugs represents a viable solution as aspects of the pharmacology of these drugs are known. With regards to COVID-19, chloroquine (CQ) and hydroxychloroquine (HCQ) have been identified as possible therapeutic agents potentially useful in combating COVID-19. Two recent studies looking at the *in vitro* antiviral effect of CQ and HCQ on SARS-CoV-2 suggest that they both can inhibit SARS-CoV-2 infection, with CQ's immunomodulatory properties enhancing its antiviral capacity.[1,2]

The quinine analogue, CQ received little attention initially due to toxicity in humans. HCQ, a derivative of CQ, was subsequently synthesized and is less toxic. Both CQ and HCQ are not new and have been on the market for a while, initially for the treatment of malaria and presently also for the management of rheumatoid arthritis and systemic lupus erythematosus.

At face value, repurposing these drugs may seem like a straightforward 'quick-fix', but this is not the case. In fact, it is a complex process from both a clinical and a regulatory perspective, requiring careful planning and assessment by clinicians, scientists, and regulatory authorities. Repurposing drugs may require deviation from the approved dosing regimens and prescribing practice in order for them to be tailored to the new disease. Such deviations give rise to more complex issues, particularly those associated with side effects and toxicity induced by the new dosing regimens. One such side effect that is of particular interest with regards to quinolone-based drugs are cardiac safety and toxicity.

Quinolone and structurally related compounds have long been known to cause cardiovascular side effects. Many antimalarial drugs cause hypotension and can alter depolarization and repolarization of cardiac and skeletal muscle.[3] It has long been known that quinolone-based drugs and their derivatives have a preponderance for causing cardiac rhythm abnormalities, giving rise, in mild cases, to transient arrhythmic episodes and, in severe cases, fatal arrhythmic events. The risks of fast intravenous injection of quinine, the striking prolongation of the electrocardiographic (ECG) QT interval triggered by quinidine, and the lethality of CQ in overdose have separately caused substantial concern.[3]

Cardiac safety studies, particularly the electrophysiological implications for CQ and HCQ, have predominantly been evaluated on the basis of its use as an antimalarial treatment and prophylactic. Characterizing the cardiac electrophysiological effects of a drug, particularly during acute illness, is not straightforward,[3] and is a major consideration during drug development.

Importantly, regulatory guidelines for the classification of drug-induced proarrhythmic tendencies do not wholly take into consideration arrhythmogenic mechanisms.[4,5] This stems directly from drug safety advice primarily based on the presence or absence of QT interval prolongation reflecting action potential duration (APD). Drugs that cause QT interval prolongation lead to life-threatening tachyarrhythmias in only a small proportion of patients.[3,6] Fatal tachyarrhythmias can also occur in individuals whose QT intervals are within the normal range. The QT interval, although important, concerns only one of the several indicators of arrhythmic tendency, namely the APD, even excluding contributions from the cardiac effective refractory period (ERP). Studies have shown that there is a positive time difference between the APD and ERP that determines arrhythmic tendency, and this cannot be measured with the QT interval only.[7]

This over-reliance on QT intervals as a cardiac safety marker lacks precision and discounts other possible mechanisms for arrhythmia including alterations in conduction velocity and calcium homeostasis in cardiac myocytes.[4] When looking to repurpose CQ and HCQ for managing COVID-19 patients, it is essential that the above electrophysiological implications are taken into consideration. Whilst regulatory guidelines for cardiac safety have evolved to encompass other proarrhythmic mechanisms, initial approval for CQ and HCQ pre-dates such regulatory changes.

Principally relevant to the pandemic at hand is that a large proportion of patients hospitalized for COVID-19 either have an underlying health condition (such as a cardiovascular disease) or are elderly, and potentially both. This gives rise to confounding factors when using CQ or HCQ for the acute management of COVID-19 infection. One study assessing the safety of CQ observed a tendency to tachycardia, but with no significant differences in mean heart rate before and after CQ administration.[8] Whilst a tendency to tachycardia would not be a major concern in an otherwise healthy patient, the same cannot be said for an elderly COVID-19 patient with an underlying health condition. It is worth highlighting that the authors of the studies assessing the *in vitro* antiviral effect of CQ and HCQ point out that the relatively low safety index of these drugs warrants a cautious approach when designing any clinical trials.[1,2]

An open-label non-randomized clinical trial suggested that HCQ treatment reduces viral load in COVID-19 patients, and this effect is reinforced using azithromycin.[9] The trial, however, involved patients with a mean age of 45.1 years (with the HCQ patient population having a mean age of 51.2 years).[9] Case fatality rates (CFRs) by age, based on data from Italy and China, however, suggest that individuals above 60 years are most affected, with CFR increasing with age.[10] There is no doubt that a more aggressive approach to treatment such as experimental therapies may be needed in COVID-19 patients. Nonetheless, a cost–benefit analysis particularly taking into account adverse cardiac events in elderly patients should inform clinical decision-making. The authors of this open-label trial allude to the fact that the potential risk of severe QT prolongation induced by the two drugs has not been established yet and should be considered.[9]

The battle to cure COVID-19 is real, but realistic expectations as to the timeline for a cure must also prevail. Politicians, clinicians, and scientists must be cautious with their claims of identifying a cure, but this should also not limit the ability to explore and test new approaches or drugs. Messaging in the era of social media can have both positive and negative consequences. The recent death of an individual who consumed CQ in the USA highlights the extent to which some of us may resort to self-medication in crisis situations based on tentative claims made by individuals or groups.

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Kamalan Jeevaratnam[1,2]*

[1]Faculty of Health and Medical Sciences, University of Surrey, Guildford GU2 7AL, UK; and [2]Physiological Laboratory, University of Cambridge, Cambridge, UK

* Corresponding author. Tel: +44 1483 682395, Email: drkamalanjeeva@gmail.com