**Type of article:** Medical students speak (Student’s corner)

**Title:** Uncontrolled mass use of hydroxychloroquine

**Running title:** Use of HCQ in COVID-19

**Authors:** Vityala Yethindra1\*

**Affiliations:** 1MBBS 4th year and Young scientist, International Higher School of Medicine, International University of Kyrgyzstan, 1F, Intergelpo Street, Bishkek, 720054, Kyrgyzstan.

**\*Corresponding author:** Vityala Yethindra

**Address:** 11-25-1013, Mattewada, Warangal urban, 506001, Telangana, India.

**Tel:** +91 91219 25658

**E-mail:** yethindravityala10@gmail.com

**Abstract**

Hydroxychloroquine (HCQ) has previously been shown to inhibit coronavirus replication in vitro. However, results from preliminary clinical studies have drawn inconclusive results regarding the efficacy of HCQ in coronavirus disease 2019 (COVID-19), due to several important weaknesses in research methodologies. Recently, serious adverse effects have been reported in patients with COVID-19. Moreover, the wide use of HCQ, even against medical advice, may have an impact on ongoing clinical trials. Currently, only doctors should be allowed to prescribe HCQ, and treatment should be restricted to hospital settings, with adequate cardiac and therapeutic drug monitoring.

**Keywords:** Hydroxychloroquine, coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2, hypokalemia.

1. **Introduction**

In addition to being an antimalarial drug, hydroxychloroquine (HCQ) also exhibits anti-inflammatory and immunomodulatory activity by regulating the production of tumor necrosis factor-alpha (TNFα), interferons, and some cytokines (1, 2). HCQ has been shown to inhibit replication in a variety of viruses (3). Although the mechanisms of these antiviral properties are not well understood, HCQ is a weak base that accumulates in lysosomes, modifies their pH, and interferes with certain enzymes.

Thus, HCQ can inhibit the pH-dependent entry of some viruses into host cells, or even block the replication of enveloped viruses by inhibiting the glycosylation of envelope proteins (4). These in vitro antiviral effects suggest the potential use of HCQ in the treatment of viral infections, against which there are no effective drugs, or against which drugs exist but are not widely available, especially in low-income countries (5).

1. **Risks of uncontrolled mass use**

In the absence of evidence of efficacy, the first potential risk is to unnecessarily expose patients to adverse effects. The most common side effects are abdominal pain or diarrhea, which is described in almost 10% of patients as well as pruritus and rashes. Headache, ringing in the ears, dizziness, and tinnitus have also been reported. Additionally, adverse psychiatric effects ranging from anxiety disorders and insomnia to psychotic decompensations have also been reported. Psychotic side effects, such as hallucinations and delusions, seem more frequent than thymic disorders (e.g., depression). Serious psychiatric effects resulting from HCQ treatment are relatively rare within the framework of conventional prescription. However, in the current context, with the anxiety-provoking nature of the coronavirus disease 2019 (COVID-19) pandemic and the desire to limit the spread of the disease, the prevalence of these undesirable effects is likely to increase.

HCQ also induces adverse cardiac effects due to its inhibitory effect on the human ether-a-go-go-related gene (hERG) potassium channels, which repolarize phase 3 cardiomyocyte action potentials in potassium efflux (potassium current IKr). This effect increases the risk of a prolonged corrected QT interval (QTc) on a surface electrocardiogram (ECG) (6). Although this toxicity is dose-dependent and therefore more frequent in the event of an overdose, cases of serious arrhythmias have been reported at therapeutic doses. Risk factors for QTc prolongation that can facilitate or precipitate such arrhythmias include a slow heart rate (<55 bpm) and female sex (7). as well as hypokalemia in combination with other drugs that lengthen the QTc.

Hypokalemia often occurs in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), possibly due to the particular tropism of SARS-CoV-2 with regard to angiotensin-converting enzyme 2 (ACE2) (8). Additionally, diarrhea and vomiting may accompany the infection. It is therefore essential to monitor serum potassium levels and correct any hypokalemia before HCQ treatment, which can itself cause diarrhea. Similarly, the combination of azithromycin, which causes QT prolongation, with HCQ, justifies reinforced monitoring with ECGs, if possible, before the start of treatment and within 3-4 h after the administration of the first dose. This should then be monitored twice a week for the duration of treatment or in the event of symptoms suggestive of dysrhythmia.

Another dose-limiting adverse effect of HCQ is the risk of retinopathy, which may potentially affect up to 8% of treated patients, especially at high doses (> 5 mg/kg) or prolonged treatment (> 5 years) (9).

Finally, since HCQ is metabolized by certain cytochrome P450 (CYP) isoforms, especially 3A4/5, 2D6, and 2C8, there is an increased risk of adverse effects with drugs that inhibit these CYPs. In the context of COVID-19, special care must be taken with other anti-infectives, such as the combination of lopinavir and ritonavir, the latter being a powerful inhibitor of CYP3A. In France, several cases of serious adverse cardiac effects have been linked to the use of HCQ in COVID-19 patients.

Remdesivir showed inhibition against severe acute respiratory syndrome coronavirus (SARS-CoV) and middle-east respiratory syndrome coronavirus (MERS-CoV) in human airway epithelial cells, at early stages of replication by inhibiting viral RNA synthesis (10). The combination of lopinavir and ritonavir, a strategy that has been used for many years to treat patients with HIV; lopinavir and ritonavir combination in the presence of interferon-β, an immunomodulatory and antiviral drug, and HCQ. In this study, treatment with one of these drugs in the 29 days preceding randomization was a criterion for non-inclusion. The inability to quickly conclude the effectiveness of these different treatments would be extremely detrimental to public health. In the context of a pandemic, it is difficult to correctly conduct randomized controlled trials until such pandemics are brought under control.

1. **Use of HCQ in COVID-19**

In the current context of the COVID-19 pandemic, in vitro data have shown that HCQ has some antiviral activity against SARS-CoV-2 compared to other drugs, with a lower half-maximal effective concentration (EC50) for HCQ (0.72 µM vs. 5.47 µM), suggesting that it is more potent (11).

HCQ should not be used, except in severe cases where patients have been hospitalized, and based on decisions made by doctors and under strict medical supervision. HCQ should not be prescribed to the general population or for non-life threatening cases of COVID-19.

HCQ is also recommended for the treatment of autoimmune diseases (12). Within the framework of the management of COVID-19, a high variability in concentrations is expected in the light of the populations likely to be treated (i.e., elderly, resuscitation, or dialysis patients) (13). In addition, given the short duration of the proposed treatment, steady-state concentrations may not be reached, thereby increasing pharmacokinetic variability.

Based on our findings, we estimated that the minimum threshold to be reached was 0.1 µg/mL for a plasma assay and 0.3 µg/mL for a total blood assay. These values may change depending on future data.

1. **Concluding remarks**

HCQ showed in vitro activity against SARS-CoV-2 and high-quality randomized controlled clinical trials are now underway. It is essential that we are able to include COVID-19 patients in these clinical trials to generate reliable data regarding drugs that show promising efficacy against COVID-19.

The absence of evidence of possible benefits must be weighed against the known adverse effects of HCQ. Although it is relatively well tolerated at therapeutic doses and for a short time, it is a drug with a narrow therapeutic window and one that requires cardiac and pharmacological monitoring to limit the serious adverse effects already reported in COVID-19 patients. This is particularly true considering polypharmacy, especially with azithromycin. Therefore, HCQ treatment must be limited to use in clinical environments and under appropriate supervision.

1. **Acknowledgements**

Nil

1. **Funding**

This work did not receive any financial assistance.

1. **Conflict of interest**

The author declares no conflicts of interest.

1. **References**
2. Weber SM, Levitz SM. Chloroquine interferes with lipopolysaccharide-induced TNF-alpha gene expression by a nonlysosomotropic mechanism. J Immunol. 2000;165(3):1534-40.
3. Müller-Calleja N, Manukyan D, Canisius A, Strand D, Lackner KJ. Hydroxychloroquine inhibits proinflammatory signaling pathways by targeting endosomal NADPH oxidase. Ann Rheum Dis. 2017;76(5):891-7.
4. Miller DK, Lenard J. Antihistaminics, local anesthetics, and other amines as antiviral agents. Proc Natl Acad Sci USA. 1981;78(6):3605-9.
5. Savarino A, Di Trani L, Donatelli I, Cauda R, Cassone A. New insights into the antiviral effects of chloroquine. Lancet Infect Dis. 2006;6(2):67–9.
6. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases. Lancet Infect Dis. 2003;3(11):722-7.
7. Borsini F, Crumb W, Pace S, Ubben D, Wible B, Yan GX, et al. In vitro cardiovascular effects of dihydroartemisin-piperaquine combination compared with other antimalarials. Antimicrob Agents Chemother. 2012;56(6):3261-70.
8. Drici MD, Clément N. Is gender a risk factor for adverse drug reactions? The example of drug-induced long QT syndrome. Drug Saf. 2001;24(8):575-85.
9. French Society of Pharmacology and Therapeutics. ACE2, IEC/ARAII and COVID-19 infections. Therapies 2020. <https://www.em-consulte.com/em/covid-19/IEC-ARA2-et-COVID19-22-mars-2020.pdf>.
10. Jorge A, Ung C, Young LH, Melles RB, Choi HK. Hydroxychloroquine retinopathy - implications of research advances for rheumatology care. Nat Rev Rheumatol. 2018;14(12):693-703.
11. Yethindra V. Role of GS-5734 (Remdesivir) in inhibiting SARS-CoV and MERS-CoV: The expected role of GS-5734 (Remdesivir) in COVID-19 (2019-nCoV) - VYTR hypothesis. IJRPS. 2020; 11: 1-6.
12. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020;ciaa237.
13. Mok CC. Therapeutic monitoring of the immuno-modulating drugs in systemic lupus erythematosus. Expert Rev Clin Immunol. 2017;13(1):35-41.
14. Guilhaumou R, Benaboud S, Bennis Y, Dahyot-Fizelier C, Dailly E, Gandia P, et al. Optimization of the treatment with beta-lactam antibiotics in critically ill patients-guidelines from the French Society of Pharmacology and Therapeutics (Société Française de Pharmacologie et Thérapeutique-SFPT) and the French Society of Anaesthesia and Intensive Care Medicine (Société Française d'Anesthésie et Resuscitation-SFAR). Crit Care. 2019;23(1):104.