Novel Approach for Low-Dose Pulmonary Delivery of Hydroxychloroquine in COVID-19

Running Title: Inhaled or nebulized hydroxychloroquine for COVID-19

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Word Count: 937

Acknowledgements: None

Declarations of Interests: The authors declare that they have no conflict of interest regarding this submission and remain neutral with regards to jurisdictional claims and institutional affiliations.

Keywords: Respiratory pharmacology, Drug delivery, COVID-19, Hydroxychloroquine, Chloroquine, Nebulization

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Dear Editor,

Despite inconclusive evidence, chloroquine (CQ) and hydroxychloroquine (HCQ) are commonly used for the treatment of Coronavirus Disease 2019 (COVID-19) in critically ill patients. The widespread use of HCQ has had unintended consequences on the healthcare system by precipitating an increased need for cardiac monitoring (due to QTc prolongation) and straining the medication’s existing supply chain [Chorin, Dai, et al. (2020); Jakhar & Kaur (2020)]. In addition, numerous trials have demonstrated marked QTc prolongation (>500 ms) and trends towards higher lethality, especially when administered in larger doses (600mg/day HCQ; 450-1200mg/day CQ) [Borba, Val, et al. (2020); Chorin, Dai, et al. (2020); Mahevas, Tran, et al. (2020)]. This is of particular concern in the critically ill COVID-19 patient, who is likely elderly, has multiple medical comorbidities, may be taking other QTc-prolonging medications (i.e. azithromycin), and may have myocarditis secondary to viral infection [Arentz, Yim et al. (2020)]. Taken together, strategies that mitigate the risk of CQ/HCQ-related systemic adverse effects should be pursued in the critically ill COVID-19 population.

With respect to the treatment of COVID-19, CQ/HCQ are thought to block proteolytic processing and endosomal acidification, effectively inhibiting autophagosome-lysosome fusion, inactivating enzymes required for viral replication, inhibiting formation of viral proteins, and blocking viral entry into host cells [Sanders, Monogue et al. (2020)]. Furthermore, these drugs may decrease cytokine production, which may provide further theoretical benefits, as hyperinflammation is implicated in COVID-19’s pathogenesis. It remains unclear to what degree each of these mechanisms contributes to the potential clinical benefit of CQ/HCQ and whether the immunomodulatory effects need to be systemic or can be localized to the lungs. Given that COVID-19 replicates chiefly within the pulmonary system and induces significant morbidity
through the pro-inflammatory cascade of Adult Respiratory Distress Syndrome, many have hypothesized that the anti-inflammatory effects of CQ/HCQ may be most beneficial when targeted within lung tissues [Frie & Gbinigie (2020)].

As an alternative to high-dose (200-600mg) oral therapy, we propose low-dose (10-20mg) delivery of water-soluble hydroxychloroquine sulfate (HCQS) via controlled nebulization or inhalation using metering valves and commercially available metered-dose inhalers. As the EC$_{50}$ of HCQ against SARS-CoV-2 is 6.14 μM, physiologically-based pharmacokinetic modeling demonstrates that an effective oral HCQ dose is 400mg twice daily for one day followed by a maintenance dose of 200mg twice daily for four days [Yao, Ye et al. (2020)]. Given that the recommended maintenance dose of HCQ is 6.4mg/kg/day and that the collective weight of the lungs is ~1kg, 10-20mg/day of inhaled HCQS (equivalent to 7.7-15.7mg/day free base) is a suitable alternative to the presently utilized orally-administered dosing regimens [McChesney, Banks et al. (1967); Yao, Ye et al. (2020)].

This lower inhaled dose is possible due to the large volume of distribution (44,257 L) for orally administered HCQ [Browning (2014)]. When given orally, only a small fraction of the drug is delivered to the lungs, while the remainder deposits in other tissues and may cause unintended adverse effects. Drug administration via nebulization allows direct delivery to lung alveoli and pulmonary tissues to elicit local effects, necessitating far lower doses than those used orally. Pharmacokinetically, HCQ remains largely neutral at physiological pH and can freely diffuse into cells and lysosomes. Upon encountering the acidic pH (4.5-5.0) of lysosomes, it is protonated into its ionized state, becoming membrane-impermeable and effectively “trapped” in
the lysosome [Browning (2014)]. This phenomenon greatly limits systemic exposure from inhaled or nebulized HCQ.

The potential benefits of this delivery modality are numerous. Cardiotoxicity and QTc prolongation from oral administration of HCQS may be circumvented with targeted pulmonary delivery, reducing the need for inpatient cardiac monitoring in an already overburdened healthcare system [Chorin, Dai et al. (2020)]. Higher lung-tissue concentrations of HCQ may be achieved via this route, potentially increasing the therapeutic efficacy of the drug while minimizing systemic adverse effects, including potentially fatal cardiac arrhythmia in at-risk patients. Furthermore, by using far lower doses of HCQ via pulmonary delivery, concerns regarding drug shortages for patients previously prescribed HCQ for rheumatic conditions may be alleviated [Jakhar & Kaur (2020)].

Although aerosolized HCQ represents a novel route of administration in COVID-19, targeted pulmonary delivery of HCQ has been previously studied for various conditions involving the upper respiratory system and bronchial tree. In animal models, aerosolized HCQ has been shown to be both safe and efficacious in the management of reactive airway disease [(Charous, Nemeth et al. (2001); Barrett, Rudolph et al. (2008)]. In 2004, Charous described inhalation of HCQ for the prophylaxis and treatment of adenovirus and rhinovirus in humans [Charous 2004]. Aerosolized HCQ has also been investigated in human trials for the treatment of moderate-persistent asthma. Following Phase 2a clinical trials in asthmatic patients, nebulized HCQ did not meet the pre-specified clinical efficacy endpoints but was found to be safe, with no serious adverse events reported [Aradigm 2006]. While these findings suggest that aerosolized HCQ
may be of minimal benefit in the treatment of asthma, they demonstrate that pulmonary delivery is a viable route that, given the mechanism by which HCQ impair in vitro the terminal glycosylation of ACE2, it might be a potent inhibitors of SARS-CoV-2 infections and prove efficacious in treatment of COVID-19. ?? acts against SARS-CoV-2, may prove efficacious in the treatment of COVID-19. After reviewing the prior literature, Klimke et al. tested the safety and tolerability of inhaled HCQ in two healthy human subject by dissolving it in 0.9% sodium chloride and administering it with a commercial nebulizer. Doses began at 1 mg twice daily and increased in a stepwise fashion to 4 mg/day over a period of one week. Outside of a transient bitter taste following inhalation, nebulized HCQ was well-tolerated without relevant adverse effects [Klimke, Hefner, et al. (2020)].

HCQS inhalation solution can be routinely prepared in hospital pharmacies by combining sterile HCQS powder with either sterile water or 0.9% sodium chloride (0.5% weight/volume) as a vehicle under aseptic conditions. This concentration can be achieved due to the high water solubility of HCQS [Pauli, Joshi et al. (2020); “Plaquenil” (2006)]. Benzalkonium chloride (0.01% or 0.1 mg/mL), a component of several FDA-approved products with clinically demonstrated safety at 0.01%, (no disruption mucociliary clearance or irritation) can be added to the solution as a preservative [Woolf & Manzi (2020)]. The resulting mixture can be used as stock solution from which doses may be administered at volumes deemed appropriate by treating clinicians. Generally, 3-5 mL may be given by nebulization or inhalation in a closed environment, with a loading dose of twice daily inhalation on the first day of therapy. Subsequently, once daily dosing of 3-5 mL should suffice, as HCQS has both a half-life and tissue residence time of at least 40 days [Browning (2014)].
In light of the consequences seen with widespread use of high-dose, orally-administered HCQ in the treatment of COVID-19, clinical testing of the pharmacological parameters of inhaled or nebulized HCQ should be a high priority. It should be noted that the authors are not advocating for the use of HCQ in treating COVID-19, as the existing clinical evidence is inconclusive and limited by study design. However, if HCQS is to be administered in critically ill COVID-19 patients, low-dose inhaled or nebulized therapy may confer the collective benefits of similar or greater drug concentrations in pulmonary tissues, less systemic adverse effects, decreased burden on the healthcare system, and diminished strain on the existing supply of hydroxychloroquine.

**Abbreviations:** QTc Interval – Corrected QT Interval; COVID-19 – Coronavirus Disease 2019; CQ – Chloroquine; HCQ – Hydroxychloroquine; HCQS – Hydroxychloroquine Sulfate; Severe Acute Respiratory Syndrome Coronavirus 2 – SARS-CoV-2; Food and Drug Administration – FDA

**References:**


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