LETTER TO THE EDITOR

Novel approach for low-dose pulmonary delivery of hydroxychloroquine in COVID-19

Dear Editor,

Despite inconclusive evidence, chloroquine and hydroxychloroquine are commonly used for the treatment of Coronavirus Disease 2019 (COVID-19) in critically ill patients. The widespread use of hydroxychloroquine has had unintended consequences on the healthcare system by precipitating an increased need for cardiac monitoring and straining the medication's supply chain (Chorin et al., 2020). In addition, numerous trials have demonstrated marked QTc interval prolongation (>500 milliseconds) and trends towards higher lethality, especially when administered in larger doses (600mg/day hydroxychloroquine; 450-1200mg/day chloroquine) (Chorin 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. Taken together, strategies that mitigate the risk of chloroquine/hydroxychloroquine-related systemic adverse effects should be pursued in this patient population.

In COVID-19, chloroquine/hydroxychloroquine are thought to block proteolytic processing and endosomal acidification, inhibit autophagosome-lysosome fusion, inactivate enzymes required for viral replication, inhibit formation of viral proteins, and block viral entry into host cells through impairment of terminal glycosylation of the ACE2 enzyme (Frie & Gbinigie, 2020). Furthermore, these drugs may decrease cytokine production, which may provide further 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 chloroquine/hydroxychloroquine 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 Acute Respiratory Distress Syndrome, many have hypothesized that the anti-inflammatory effects of chloroquine/hydroxychloroquine 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 via controlled nebulization or inhalation using metering valves and commercially available metered-dose inhalers. As the EC_{50} of hydroxychloroquine against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is 6.14 μM, physiologically-based pharmacokinetic modelling demonstrates that an effective oral hydroxychloroquine dose is 400mg twice daily for one day, followed by a maintenance dose of 200mg twice daily for four days (Yao et al., 2020). Given that the recommended maintenance dose of hydroxychloroquine is 6.4mg/kg/day and that the collective weight of the lungs is ~1kg, 10-20mg/day of inhaled hydroxychloroquine sulfate (equivalent to 7.7-15.7mg/day free base) is a suitable alternative to the presently utilized orally-administered dosing regimens (Yao et al., 2020).

This lower inhaled dose is possible due to the large volume of distribution (44,257 L) for orally administered hydroxychloroquine (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, hydroxychloroquine 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 hydroxychloroquine.

The potential benefits of this delivery modality are numerous. Cardiotoxicity and QTc prolongation from oral administration of hydroxychloroquine sulfate may be circumvented with targeted pulmonary delivery, reducing the need for inpatient cardiac monitoring in an already overburdened healthcare system (Chorin et al., 2020). Higher lung-tissue concentrations of hydroxychloroquine 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 hydroxychloroquine via pulmonary delivery, concerns regarding drug shortages for patients previously prescribed hydroxychloroquine for rheumatic conditions may be alleviated.

Targeted pulmonary delivery of aerosolized hydroxychloroquine has been previously described for various respiratory conditions, with Phase 2a clinical trials in asthmatic patients demonstrating no adverse events (Aradigm, 2006). A recent study on inhaled hydroxychloroquine at doses of up to 4 mg/day found that the drug was well-tolerated outside of a transient bitter taste following inhalation (Klimke, Hefner, Will, & Voss, 2020). Although further evidence is needed to determine the efficacy of aerosolized hydroxychloroquine in the treatment of COVID-19, low-dose targeted pulmonary delivery represents a safe and potentially preferred delivery method, particularly given the purported mechanisms by which hydroxychloroquine acts against SARS-CoV-2.
Hydroxychloroquine sulfate inhalation solution can be routinely prepared in hospital pharmacies by combining sterile hydroxychloroquine sulfate powder with either sterile water or 0.9% sodium chloride (0.5% weight/volume) as a vehicle under aseptic conditions. Benzalkonium chloride (0.01% or 0.1 mg/mL), a component of several FDA-approved products with clinically demonstrated safety at 0.01%, can be added to the solution as a preservative. 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 hydroxychloroquine sulfate 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 hydroxychloroquine in the treatment of COVID-19, clinical testing of the pharmacological parameters of inhaled or nebulized hydroxychloroquine should be a high priority. It should be noted that the authors are not advocating for the use of hydroxychloroquine in treating COVID-19, as the existing clinical evidence is inconclusive and limited by study design. However, if hydroxychloroquine 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 (including cardiotoxicity), decreased burden on the healthcare system, and diminished strain on the existing supply of hydroxychloroquine.

CONFLICT OF INTEREST

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

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REFERENCES


