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Safety, Tolerability, and Pharmacokinetics of Nebulized Hydroxychloroquine: A Pilot Study in Healthy Volunteers

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Abstract

Background: Early in the coronavirus disease 2019 (COVID-19) pandemic, hydroxychloroquine (HCQ) drew substantial attention as a potential COVID-19 treatment based on its antiviral and immunomodulatory effects *in vitro*. However, HCQ showed a lack of efficacy *in vivo*, and different groups of researchers attributed this failure to the insufficient drug concentration in the lung following oral administration (HCQ is only available in the market in the tablet form). Delivering HCQ by inhalation represents a more efficient route of administration to increase HCQ exposure in the lungs while minimizing systemic toxicity. In this pilot study, the safety, tolerability, and pharmacokinetics of HCQ nebulizer solution were evaluated in healthy volunteers.
Methods: Twelve healthy participants were included in this study and were administered 2 mL of HCQ01 solution (equivalent to 25 mg of HCQ sulfate) through Aerogen® Solo, a vibrating mesh nebulizer. Local tolerability and systemic safety were assessed by forced expiratory volume in the first and second electrocardiograms, clinical laboratory results (e.g., hematology, biochemistry, and urinalysis), vital signs, and physical examinations. Thirteen blood samples were collected to determine HCQ01 systemic exposure before and until 6 hours after inhalation.
Results: The inhalation of HCQ01 was well tolerated in all participants. The mean value of C_{max} for the 12 participants was 9.66 ng/mL. T_{max} occurred at around 4.8 minutes after inhalation and rapidly decreased thereafter. The reported systemic exposure was very low with a mean value of 5.28 (0.6–15.6) ng·h/mL.
Conclusion: The low systemic concentrations of HCQ01 of 9.66 ng/mL reported by our study compared with 1 μg/mL previously predicted after 200 mg BID oral administration, and the safety and tolerability of HCQ01 administered as a single dose through nebulization, support the assessment of its efficacy, safety, and tolerability in further studies for the treatment of COVID-19.

Keywords: inhalable hydroxychloroquine, lung diseases, nebulizer, pharmacokinetics, phase I study

Introduction

In late December 2019, an outbreak of a novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in China's Wuhan State,[1] and has since had devastating consequences worldwide. As of August 16, 2022, after more than 2.5 years since the beginning of the pandemic, 591,683,619 confirmed cases of COVID-19, including 6,443,306 deaths have been reported worldwide.[2]

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Vaccination is considered one of the most promising and effective approaches for curbing the COVID-19 pandemic. Several COVID-19 vaccines have been developed and have been highly effective in reducing the risk of severe illness, hospitalization, and death from COVID-19.[3,4] Nevertheless, despite the availability of many safe and effective vaccines, controlling the transmission of SARS-CoV-2 has proven to be elusive for several reasons, including the global vaccine supply shortages and the inequitable vaccine distribution among low- and middle-income countries,[5] vaccine hesitancy,[6] and the emergence of new variants.[7]

Today, several therapeutic options are available to treat COVID-19 in outpatient and hospitalized settings, including antivirals and immunomodulatory drugs. These two major groups target two different clinical phases of COVID-19; the early phase and the late phase. The early phase is predominated by viral replication, while the late phase is associated with imbalanced inflammatory reaction and biased immune system, with antiviral and immunomodulatory therapies being more effective in the early and late phases, respectively. Given that viral replication is particularly active early in the course of COVID-19, antiviral therapy may have the greatest impact before the illness progresses to the hyperinflammatory state that can feature the later stages of disease, including critical illness.[8] Remdesivir is the only antiviral drug that is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19. Ritonavir-boosted nirmatrelvir (Paxlovid) and molnupiravir have received emergency use authorizations from the FDA for the treatment of COVID-19.[9–11]

Taken together, there is thus still an urgent need for identifying different therapeutics, including effective antivirals to reduce SARS-CoV-2 morbidity and mortality rate and to control its spread.

The emergence of the outbreak has driven a massive search and investment to find effective treatments and has likewise encouraged the off-label testing of repurposed drugs that are licensed or currently under investigation. The main advantages of drug repurposing over new discoveries include the availability of information about human pharmacokinetics (PK), pharmacodynamics, and toxicity of the potential drugs as well as the preclinical results,[12] lack of patent protection for these approved drugs, accelerated approval time lines (require less time and tests and can enter directly preclinical testing and clinical trials), and established manufacturing systems.[13]

Since the beginning of the pandemic, several potential antiviral drugs have been investigated against the SARS-CoV-2 infection. One of these drugs is hydroxychloroquine (HCQ), an approved antimalarial agent that is still widely used for treating systemic autoimmune diseases (e.g., systemic lupus erythematosus and rheumatoid arthritis) due to its immunomodulatory properties.[14] Early in the pandemic, HCQ drew substantial attention as a potential molecule to prevent and treat COVID-19 due to both its antiviral and immunomodulatory effects.

HCQ showed *in vitro* antiviral activity against SARS-CoV-2.[15,16] Specifically, it was proposed that, in COVID-19, HCQ could 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.[17] Furthermore, given the reported status of hyperinflammation in COVID-19 patients, especially those with severe cases,[18,19] HCQ was also proposed as a promising anti-inflammatory candidate that could target the key cytokines involved in COVID-19, help tip the immune response toward a less inflammatory state, and reduce evolution into cytokine storm.

Despite the promising results of HCQ in laboratory cell-based studies,[15,16] and in some observational studies,[20–23] larger randomized controlled clinical trials, namely the U.K. RECOVERY trial and the WHO SOLIDARITY trial[24,25] stopped enrollment into their HCQ treatment arms due to lack of effects on the 28-day mortality rate endpoint.

To our knowledge, all clinical studies conducted on COVID-19 patients in which HCQ was administered were through oral administration (HCQ is only available in the market in tablet form). Several groups of researchers attributed the failure of the studies conducted with systemic HCQ to the insufficient therapeutic concentrations of HCQ reaching the lung tissues.[26–29] However, despite the oral dose likely being insufficient, increasing it is not an option due to toxicity concerns, including the QT interval (QTc) prolongation with subsequent fatal cardiac arrhythmias.[30,31]

Delivering HCQ by inhalation represents a more efficient route of administration to increase HCQ exposure in the lungs while minimizing systemic toxicity.[17,32,33] Other research groups have worked on inhalable products of HCQ for COVID-19 treatment,[34–37] but to date more research is needed to demonstrate the feasibility of pulmonary administration of HCQ.

To our knowledge, only three research groups have investigated the use of inhaled HCQ in healthy volunteers in phase I studies; in the first study, participants were administered HCQ dry powder per inhalation using the Cyclops device,[34] a sterile aerosolized HCQ was administered to 10 healthy volunteers in the second study through the Aerogen nebulizer,[35] while in the third study, the investigational product was HCQ liposome inhalation suspension.[38]

Our team of researchers developed a Physiologically Based Pharmacokinetic (PBPK) model of nebulized HCQ for pulmonary delivery to COVID-19 patients, to calculate the necessary inhalation dose regimen of HCQ,[26] and manufactured a sterile aqueous nebulizer solution containing 12.5 mg/mL of HCQ (HCQ01). In this report, we present our local and systemic tolerability and safety in healthy volunteers; and the concentrations of HCQ in systemic circulation following inhalation. Moreover, we compare the actual HCQ concentrations in healthy volunteers with those predicted by our PBPK model. We hope that our work will fill in the knowledge gap regarding the potential use of inhaled HCQ for the treatment of COVID-19, and encourage other working groups to proceed with more advanced clinical phases.

Materials and Methods

Study drug

Study drug development and manufacturing. HCQ nebulizer solution was developed to meet the target product profile of the drug under investigation, and the product was designed as a sterile solution having a concentration of 12.5 mg/mL in normal saline solution with a sweetening

agent added to improve taste and thus patient compliance. All ingredients were selected based on their safety and compatibility with the respiratory system.

Chemicals. Good manufacturing practice-grade (GMP-grade) hydroxychloroquine sulfate (HCQS) raw powder Batch 20077HS4RII was provided by Hikma as a gift. Sodium chloride, sucralose, and benzalkonium chloride are pure pharmaceutical grade provided by Sana Pharmaceutical Industry (Amman-Jordan).

HCQS nebulizer solution. The nebulizer solution was manufactured by a simple mixing procedure without the involvement of heat. The solution was sterilized by filtration using a 0.45/0.2 μm Sartobran filter from Sartorius and filled under aseptic conditions in a class B/A filling area. No terminal sterilization step was applied.

Chemical analysis. A validated in-house method used for the determination of HCQS content in the NEBULIZER solution by UV spectrophotometer using a 1cm quartz cell at wavelength 343 nm. HCQ impurities were detected by a thin-layer chromatography method using 0.1% sodium hydroxide silica gel G plate 20×20 cm board with a mixture of alcohol: water: ammonium hydroxide (80:16:4) v/v/v% as a mobile phase. Samples were diluted in 10% water in methanol prior application. A sample size of 20 μL was applied and allowed to spread up among the plate and dried at room temperature.

Manufacturing facility. The product was manufactured in a current good manufacturing practice (cGMP) manufacturing site approved for sterile solutions (Amman Pharmaceutical Industry, Amman, Jordan).

Phase I study

Study design. This study was an open-label, one-way, single-dose, phase I study to evaluate the safety, tolerability (local and systemic), and PK of 2 mL of HCQ01 (12.5 mg HCQS per 1 mL) in 12 nonsmokers from the Jordan populace. Participants were healthy, Caucasian adults, aged between 18 and 50 years, both inclusive, within the accepted limits for body height and weight and meeting the selection criteria for this study. The clinical conduct of the study, bioanalytical, pharmacokinetic, and statistical analyses were carried out at ACDIMA BioCenter for Bioequivalence and Pharmaceutical Studies in Amman, Jordan. This study was conducted according to the principles of Good Clinical Practice that have their origins in the Declaration of Helsinki. This study was subjected to the review and approval of ACDIMA BioCenter Institutional Review Board (IRB) and the inspection of the Jordan Food and Drug Administration. Subjects were recruited after obtaining their informed consent.

Drug administration. After an overnight fast of 10–12 hours and in the morning of the second day of study (day 2), starting from 08:00 A.M., 2 mL of HCQ01 solution (equivalent to 25 mg of HCQS) was administered by Aerogen® Solo, vibrating mesh nebulizer (Aerogen, Galway, Ireland). The selection of the administered dose was based on our previous work.[26]

Blood sampling and bioanalytical method. Thirteen PK samples were collected through an indwelling cannula into lithium heparin tubes according to the following schedule: Predosing (zero time) and 0.03, 0.08, 0.17, 0.25, 0.33, 0.42, 0.50, 1.00, 2.00, 3.00, 4.00, and 6.00 hours postdosing. Samples were analyzed according to a validated liquid chromatography tandem-mass spectrometry method developed in-house according to the ''FDA Bioanalytical Method Validation Guidance'' and the European Medical Agency ''Guideline on Bioanalytical Method Validation.'' Analysis was carried on HCQ concentrations in plasma, and the linear range used was 1.00–1000.00 ng/mL. The internal standard used was hydroxychloroquine–d4. After collection, blood samples were placed in an ice bath or another chilling device until centrifugation.

Pharmacokinetics, statistical analysis, and safety analysis. PK parameters were derived from plasma concentration-time profiles among the enrolled healthy Caucasian participants, the pharmacokinetic parameters: C_{max}, AUC_{0-t} and T_{max} were calculated for HCQ, applying noncompartmental analysis using licensed and validated Phoenix® WinNonlin® version 8.3 software. SAS 9.4 software was used for statistical analysis. Excel and Word were used for data management.

Safety assessment. Participants were monitored for any adverse events (AEs), serious adverse events (SAEs), concomitant medications, nonpharmacological treatments, and changes in clinical laboratory results, for example, spirometry, hematology, biochemistry, urinalysis, and serology, 12-lead electrocardiogram (ECG) results, clinical symptoms, vital signs, and physical examination results. All AEs were coded using the Medical Dictionary for Regulatory Activities and summarized by System Organ Class, preferred term, and treatment group.

Results

A total of 12 healthy participants were screened, enrolled, and completed the study assessments (Fig. 1). Participants' baseline characteristics are presented in Table 1.

The inhalation of HCQ01 was well tolerated in all the enrolled participants who completed the study without any

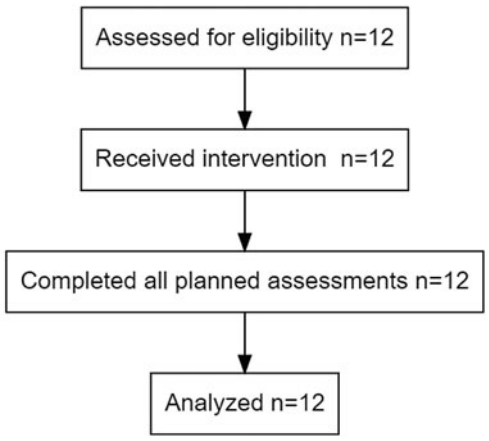

FIG. 1. Flow diagram of healthy participants planned, enrolled, and analyzed in this pilot study.

Table 1. Participants' Baseline Characteristics

HCQ01 25 mg (N = 12)	
Male, *n* (%)	12 (100.0%)
Nonsmokers, *n* (%)	12 (100.0%)
Age (years), mean (range)	29.3 (18–41)
Weight (kg), mean (range)	79.00 (60.0–90.0)
Height (m), mean (range)	1.738 (1.70–1.79)
Body mass index (kg/m^2), mean (range)	26.15 (20.8–29.4)

clinically significant changes from their baseline following the administration of 2 mL of nebulized HCQ01 solution, equivalent to 25 mg of HCQS. During the conduct of the study (time frame: 0–12 hours), there were no reported AEs or SAEs.

The mean plasma concentration–time curve of HCQ01 is presented in Figure 2, and the pharmacokinetic parameters are summarized in Table 2. In nine participants, HCQ01 was detected ≥ lower limit of quantitation (LLOQ) of 1.00 ng/mL at the first sampling time, 0.03 hour, while it was detected only in two participants at the last sampling time, 6 hours. T_{max} occurred at around 4.8 minutes after inhalation and rapidly decreased thereafter. The reported systemic exposure was very low with a mean value of 5.28 (0.6–15.6) ng·h/mL.

Discussion

The current study in healthy participants evaluated the safety, tolerability, and PK of a single dose of inhaled HCQ of 25 mg administered through nebulization. C_{max} was attained in ~0.03 and 0.17 hour after the completion of dosing (nebulization time ~5.2 minutes). The mean value of C_{max} for the 12 participants was 9.66 ng/mL. When compared with the regular 200 mg BID oral dosing that can reach more than 1 μg/mL,[26] nebulized HCQ resulted in a 100-fold lower C_{max}. However, the intersubject variability is more than 30%, which can be due to the low sample size of this pilot study.

When C_{max} of 9.66 ng/mL measured *in vivo*, data are compared with C_{max} of 10.96 ng/mL as predicted by simulation data done in GastroPlus,[26] the prediction error is 13.46%. This indicates that the inhalation model in GastroPlus was accurate.

The low systemic exposure ($AUC_{0–6}$) reported by our study was also supported by the findings of a phase I study with nebulized HCQ in 15 participants randomized into three groups to receive a single exposure of 5, 10, or 20 mg of HCQ.[33]

Local and systemic safety in addition to tolerability was assessed. As a result, no local or systemic AEs were reported throughout the conduct of the study, which was evaluated within the time frame of 0–12 hours. For safety and follow-up measures for subjects, ECG recording was performed at 2 hours postdosing. Hematology, biochemistry, urinalysis, forced expiratory volume in the first and second tests, and ECG recording, were performed at the end of clinical conduct. Variations were filled for seven subjects for having out-of-range laboratory parameters. However, reported variations were considered clinically nonsignificant by the clinical investigator. Our product HCQ01 was well tolerated by the participants.

Our study has some limitations, namely it is a small sample size. However, given the fact that there was no available information on similar formulations to guide us in power calculation, we decided that 12 participants would be sufficient to provide us with valuable insights regarding the design, conduct, and analysis for the future definitive pivotal phase, and more precise estimates for sample size calculations. Based on our PBPK model,[26] the 25 mg BID inhalation dosing for 5 days was predicted to lead to alveolar HCQ levels of 7 μM (above EC50 of ~1–5 μM). In this pilot study, we investigated the use of a single dose of nebulized HCQ of 25 mg, however, we believe that HCQ01 can be used safely for multiple dosing.

Our positive results related to the safety and tolerability of nebulized HCQ as well as the reported very low systemic exposure may encourage other researchers to proceed with more advanced clinical phases with nebulized HCQ for the treatment of COVID-19. Moreover, given the fact that nebulized HCQ has a better systemic exposure (lower C_{max}) and higher lung tissues concentrations based on our previous PBPK model,[26] we strongly believe that nebulized HCQ has other potential indications that might be attractive to the scientific community in targeting other lung diseases, including lung cancer, that have been previously investigated using the oral dosing.[39–42]

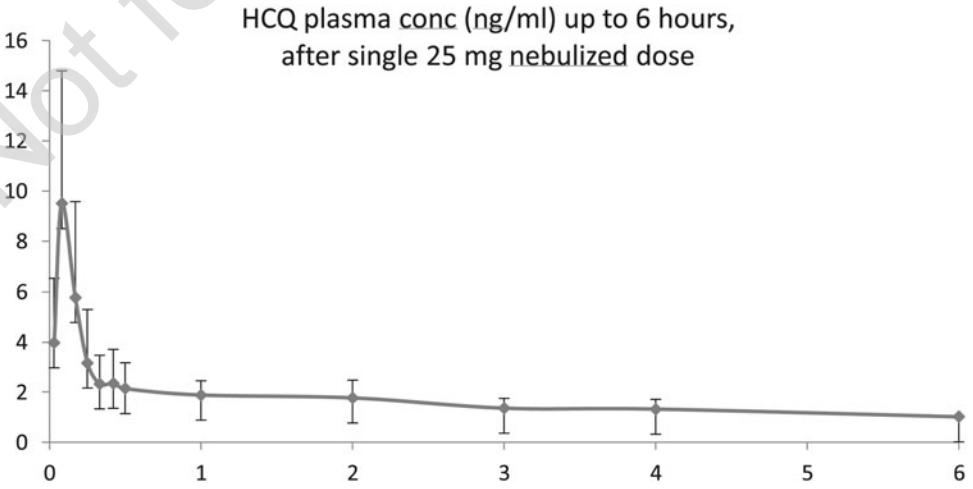

FIG. 2. The plasma profile following the administration of 2 mL nebulized dose of 12.5 mg/mL HCQ01 solution.

Table 2. Mean Pharmacokinetic Parameters of Hydroxychloroquine Following the Administration of 2 mL Nebulized Dose of 12.5 mg/mL Solution

Parameter	C_{max} *(ng/mL)*	T_{max} *(hour)*	AUC_{0-6} *(ng·h/mL)*
Mean	9.66	0.083	5.28
CV%	52.4	37.4	89.0

The contact time with levels above 1 μM was the expected 0.8–0.9 hour in any of the lung parts as per our previous simulations.[26] Indeed, the cellular uptake of chloroquine is closer to the conditions occurring *in vivo*. Under these conditions, it was possible to obtain levels of inhibition of viral replication above 90%.[43] Moreover, HCQ ability to inhibit lung viral replication was shown to be effective for a 10-day period after only a 5-day cycle of therapy.[44,45] This exposure response effect is also noticed with quinolone such as ciprofloxacin.[46]

Conclusion

The low systemic concentrations, safety, and tolerability of HCQ01 administered as a single dose through nebulization support the assessment of its efficacy, safety, and tolerability in further studies for the treatment of COVID-19.

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Author's Contributions

Conceptualization: F.H., N.I., and Y.D. Formal analysis: N.I. Investigation: R.T. and M.A.F. Product manufacturing: S.N. and H.K. Product analysis: S.N. Bioanalysis: A.A.Z. Methodology: F.H., N.I., Y.D., R.T., M.A.F., and A.A.Z. Project administration: Y.D. Supervision: F.H. Writing—original draft: N.I., Y.D., and S.N. Writing—review and editing: F.H., R.T., M.A.F., H.K., and A.A.Z.

Author Disclosure Statement

The authors declare they have no conflicting financial interests.

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