

Towards Optimization of Hydroxychloroquine Dosing in Intensive Care Unit COVID-19 Patients

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Abstract

Hydroxychloroquine (HCQ) appears to be a promising treatment for COVID-19. However, all ongoing clinical trials with HCQ use different dosing regimens, resulting on various concentrations PK studies are therefore needed to define the optimal dosing regimen.

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Introduction

Since December 2019, an outbreak of COVID-19 due to SARS-Cov-2 virus has spread from China. On March 11, 2020, the WHO described the global COVID-19 situation as a pandemic. As of March 30, 2020, no treatment has demonstrated clinical efficacy against COVID-19. However, several treatment strategies are being considered and evaluated in numerous clinical trials. Among these strategies, the use of hydroxychloroquine (HCQ) appears to be a promising option, although only limited evidence is available at the present time. Above all, HCQ has the advantage of being widely available to a large number of patients. HCQ is a well-known drug, effective in the treatment of malaria and autoimmune diseases. More recently, an *in vitro* antiviral effect has been demonstrated on SARS-Cov-2. Recent work by Wang et al. showed that a chloroquine concentration of 0.36 mg/L decreased viral load by 50% in a cell model [1].

Apart from the ongoing clinical evaluation of the efficacy of HCQ, little information is available concerning the modalities of administration of this drug for Intensive Care Unit (ICU) patients, especially in the context of COVID-19. HCQ can be responsible for adverse events and probably an increased incidence of adverse events in the case of inappropriate dosing regimens. One of the most serious adverse events in this population is cardiac toxicity, characterized by prolongation of the QT interval, which can lead to arrhythmia in patients at risk. HCQ also has very particular pharmacokinetic (PK) properties that require certain precautions. It exhibits strong tissue tropism, particularly for the kidney and liver, with a long half-life (several weeks). The risk of overdose is higher in the ICU population with impaired renal and/or hepatic function than in other populations.

To date, HCQ PK parameters have been estimated from studies in patients with rheumatoid arthritis or lupus [2] or healthy volunteers [3,4]. However, physiological changes in infused, ventilated patients with multiple organ failure may modify HCQ PK parameters. For these reasons, we conducted a prospective study to evaluate the PK properties of HCQ in ICU COVID-19 patients.

Material and Methods

Study overview

This prospective cohort study was conducted at Saint Etienne University Hospital (France) between 03/13/2020 and 03/23/2020. The study was approved by the institutional review board [IRBN462020/CHUSTE]. All consecutive patients with laboratory-confirmed SARS-CoV-2 infection treated by HCQ in the critical care unit were included.

Treatment

Patients received 200 mg of oral HCQ, three times daily, as suggested by a recent study [9]. Blood samples for determination of drug levels were drawn as part of routine care, with the decision to perform therapeutic drug monitoring based on medical guidance. HCQ trough levels >1 mg/L and <2 mg/L were considered to be therapeutic [5,6]. The medical team received all results in real time to allow for dose adjustments, as necessary.

Sample collection and analysis

Blood samples were drawn from an arterial catheter and transferred to ethylenediamine tetraacetic acid-containing tubes. HCQ blood levels were analyzed using a validated liquid chromatography-mass spectrometry method. Briefly, blood samples (200 μ L) were spiked with 200 μ L hydroxychloroquine-D4 prepared (0.2 mg/L) in 15% trichloroacetic acid, and 200 μ L zinc sulfate was used for liquid-liquid extraction. The lower limit of quantification was 0.010 mg/L.

Simulations

To more clearly understand HCQ PK and the effect of the dosing regimen, a simulation based on a PK population study in patients with rheumatoid arthritis was performed [2]. From the variance-covariance matrix of the estimated PK parameters, Monte Carlo simulations were performed using mlxplora (Lixsoft). A total of 200 patients were generated receiving different dosing regimen based on ongoing clinical trials.

Results

Population

Thirteen patients were included in this prospective PK study. The median age of patients was 68 years [38 – 82 years]. Most patients were male (85%). Median body weight was 82.7 kg [63 – 117 kg] and 46% were considered to be obese (body mass index > 30 kg/m²). Median renal function estimated by the CKD-EPI formula was 79.6 mL.min⁻¹ [12 – 118]; 30.7% of subjects presented moderate or severe renal failure. Twelve patients were mechanically ventilated. One patient was treated by ECMO and another patient was treated by renal replacement therapy.

PK analysis

A total of 161 blood levels were recorded and used for the analysis and 6 samples were below the limit of quantification of the assay (Figure 1). Only 8/13 patients (61%) achieved the supposed minimum therapeutic level of 1 mg/L and 2/13 patients exceeded a concentration of 2 mg/L. The mean time to reach the minimum therapeutic level was 2.7 days [1–4.5 days]. Four patients underwent dose de-escalation and subsequently received 200 mg of HCQ twice daily. HCQ was withdrawn in two patients: due to QT interval prolongation (381 to 510 ms and 432 to 550 ms) on day 2 and 3 with HCQ blood levels of 0.03 mg/L and 1.74 mg/L, respectively.

Simulations

The various dosing regimens used in currently recruiting clinical trials were simulated in order to determine the variability of HCQ PK parameters (Figure 2). Treatment A achieved target levels on day 3. Treatment B achieved target levels but resulted in blood levels exceeding 2 mg/L on day 3. Treatment C rapidly achieved target levels (1st dose), but blood levels exceeded 2 mg/L after 8 hours. Treatment D achieved target levels after 2.5 days and a level of 2 mg/L after 4 days. Finally, we proposed treatment D to rapidly achieve target levels without exceeding 2 mg/L.

Discussion

To our knowledge, this is the first study to describe HCQ PK in ICU patients. In this study, we demonstrated that the 200 mg three times daily dosing regimen is inappropriate to reach a supposed target blood level of 1 – 2 mg/L in this population. Using this dosing regimen, the mean time to reach therapeutic levels was more than 2 days and only 61% of patients reached target levels with this dosing regimen. This result is not surprising in view of the PK properties of HCQ [7]. HCQ presented marked PK variability with a very long half-life (5 to 40 days), particularly due to large distribution into blood and tissues. Steady-state concentrations are therefore achieved within weeks and vary from individual to individual with the same dosing regimen. However, ICU patients present certain characteristics that can affect the PK of drugs. For example, the presence of ECMO may affect the already altered PK of ICU patients by further increasing the volume of distribution, causing changes in clearance, and causing adsorption or absorption into the circuit [8]. In the one patient treated by ECMO in this study, HCQ blood levels increased more slowly than in the other patients.

The therapeutic level of HCQ in COVID-19 patients has not yet been established. Some *in vitro* and *in silico* studies have reported a virustatic effect of chloroquine and HCQ and estimated the therapeutic blood level from EC₅₀, ranging from 0.3 to 2.1 mg/L [1,5]. The toxic HCQ concentration has not been established, although a number of arguments suggest that a concentration of 2 mg/L should not be exceeded to avoid ocular toxicity. However, the most dreaded adverse effect for COVID-19 patients is cardiac toxicity. To our knowledge, the

relationship between cardiac toxicity and HCQ blood levels has not been determined, but it can be assumed that excessive HCQ exposure is likely to be harmful. In this study, two patients experienced cardiac toxicity at variable HCQ blood concentrations.

No guidelines for administration of HCQ are currently available. Using physiologically-based pharmacokinetic models, Yao et al. suggested a dosage of 400 mg twice daily for 1 day, followed by 200 mg twice daily for another 4 days [5]. This regimen could constitute an appropriate option, although the results of our study suggest that 800 mg once daily on the first day can more rapidly reach therapeutic levels in ICU patients. All of the 9 clinical trials concerning the therapeutic use of HCQ in COVID-19 registered in clinicaltrials.gov (on March 26) are using different dosing regimens. Based on our simulations, we demonstrate that some of these dosing regimens will fail to reach therapeutic levels, while others will probably induce levels higher than 2 mg/L. This work strongly suggests that the HCQ dosing regimen should be optimized on the basis of PK data available in special populations. There is an urgent need for health agencies to clarify the standard dosing regimen of HCQ in order to have comparable data across clinical trials, and to avoid dubious efficacy or toxicity results due to PK profiles.

Conclusion

Based on this prospective study, we demonstrate that PK studies are needed to define the optimal dosing regimen for ICU COVID-19 patients. Based on our simulations, we propose a loading dose of 800 mg once daily on day 1, followed by 200 mg twice daily for 7 days. Therapeutic drug monitoring should be used to personalize the optimal dosing regimen. Further PK and PD (virological) studies are also warranted.

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Figure 1. Pharmacokinetic data in critically ill patients and simulation

Red dots represent HCQ blood levels for a dosing regimen of 200 mg three times daily, triangles represent HCQ blood levels after discontinuation of treatment, circles represent HCQ blood levels for a dosing regimen of 200 mg twice daily. The green shaded zone represents the 90% simulation interval obtained with the model of Carmichael et al for HCQ 200 mg three times daily [2].

Figure 2. Hydroxychloroquine pharmacokinetic simulation

The brown line represents treatment A: 400 mg once daily for 5 days (NCT04261517). The blue line represents treatment B: 400 mg twice daily for 7 days (NCT04316377). The pink line represents treatment C: 800 mg loading dose followed by 600 mg 8 hours later and then 600 mg once daily for 4 days (NCT04308668). The red line represents treatment D: 200 mg three times daily for 7 days [9]. The green line represents the recommended treatment E: 800 mg loading dose followed by 200 mg twice daily for 6 days; the green shaded zone represents its 90% simulation interval.

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Figure 1

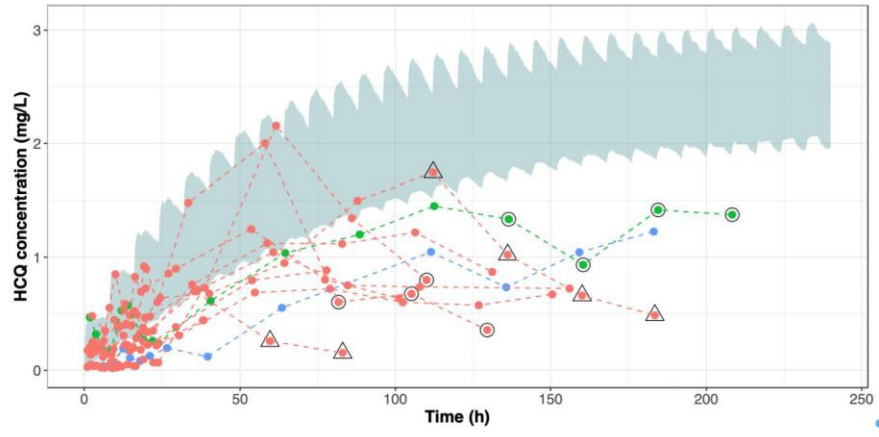


Figure 2

