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Chronic kidney failure with hydroxychloroquine

Paul Sebo1 · Sylvain de Lucia2 · Nathalie Vernaz3

Department of Pharmacological Research

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Introduction

Since March 23, 2020, patients with COVID-19 have been treated in Algeria using a treatment strategy that mostly consists of hydroxychloroquine. With a recovery rate of 98.2% out of 16,000 cases treated, this regimen has demonstrated its "almost total" efficacy [1].
Based on the findings of preliminary work by multiple teams that we previously examined with a further three-month follow-up, hydroxychloroquine (HCQ) is recommended due to its greater predicted tolerance.
At the pharmaceutical level, this molecule's pharmacology is interesting and highlights the need for pharmacokinetic investigations to determine the best dosing schedule for individuals with a specific statistic (fatty COVID-19, hepatic insufficiency, or renal insufficiency). Based on this work, dosage modifications can be suggested, and the timing of administration can be modified with therapeutic monitoring of the medications to be carried out to customize each patient's dosage regimen.In order to improve and adjust procedures by creating new prescribing protocols and making sure that adverse events are adequately controlled, the hospital pharmacist's role is crucial during a pandemic.

Case Description

This 18-year-old patient, who weighs 65 kg and has been diagnosed with COVID-19, was hospitalized to the COVID University Hospital Establishment UHE on May 11, 2020, with malformative nephropathy.
ORAN, Algeria, whose father has been confirmed to be positive after suspicion of contamination.
With diuresis of 1100 ml, arterial pressure of 120/80, temperature of 36.2 °C, and heart rate of 120 beats per minute, the patient is asymptomatic and in a generally conserved state. = 90 bpm, an oxygen saturation SAO2 = 98%, and a regular sinus rhythm (PR = 0.16 s, QRSfin, normal AXIS, QTc = 400 ms) at l'' ECG.
Following the national procedure, the patient was placed on a particular course of treatment. The latter will take the following medications: 200 mg of hydroxychloroquine three times a day for ten days, along with 250 mg of azithromycin: 500 mg on the first day and 250 mg daily for the next four days.
Given the severe renal impairment (clearance = 8 ml/min), a 50% reduction in the normal dose of HCQ to 100 mg three times a day was advised in accordance with nephrological guidance.
Following a request from the UHE Pharmacovigilance Department's Therapeutic Optimisation Unit, the clinical pharmacy team manufactured capsules with the suggested dosage in addition to a pharmaceutical analysis of the patient's prescription.
During the first five days of hospitalization, the patient's clearance progressed as follows:

Duration of hospitalization	**D1**	**D2**	**D3**	**D4**	**D5**
Clearance ml / min / 1.73 m² (MDRD)	6.28	6.1	6.51	6.91	7.31
Clearance ml / min (cockroroft)	9.73	9.49	10.09	10.57	11.09

Table I: Evolution of patient clearance during the first five days of hospitalisation

Hydroxychloroquine pharmacokinetics and toxicity profile

The ministerial protocol put up by the expert committee in reaction to the COVID-19 pandemic includes hydroxychloroquine, an anti-malarial belonging to the class of amino-4-quinolines [2]. Following oral treatment, this molecule is quickly absorbed in the digestive tract, has a wide distribution, and is very connected to plasma proteins that are widely distributed throughout the kidney, liver, lungs, and melanin-containing cells such those found in the skin and eyes. It passes via the placenta. In the liver, it is primarily converted to monodesethylchloroquine (cletoquine) and bisdesethylchloroquine. There have been reports of some activity with monodesethylcholoroquine. Renal elimination accounts for 50% of elimination in its unaltered form and 10% in its monodesethylchloroquine form. Hydroxychloroquine has a half-life of roughly 30 days. Consequently, this molecule builds up in the tissues and may be present there for a few weeks or months. It is important to consider potential pharmacokinetic medication interactions because hydroxychloroquine is a substrate for CYP2C8, CYP3A4, and CYP2C6 [2, 3].

Retinopathies, hemolytic anemia, porphyria, G6PD deficiency, and myasthenia gravis are among the contraindications [3].

- Headache, rash, pruritus, gastrointestinal problems (diarrhea, vomiting, and nausea), vision abnormalities, and cardiomyopathy are the most common side effects of hydroxychloroquine. It has been noted that these side effects are more common and severe at large dosages and over an extended period of time.

Retinal toxicity is dependent on patient risk factors, cumulative dose (>1000g), daily dose (>400mg/J), and treatment duration (>5 years).

- Because of the brief length of therapy, retinal toxicity is not questioned in this experimental setting (10J).
- Cardiac toxicity: Hydroxychloroquine causes a negative inotropic action, inhibits spontaneous diastolic depolarization, slows conduction, lengthens the effective refractory period, and raises the electrical threshold. This action is comparable to that of quinidine. This leads to a decrease in excitability, a change in conductivity, a depression of contractility, and perhaps an aberrant stimulus that triggers reentry mechanisms. The initial sign of an overdose may be cardiac arrest. There is a correlation between the degree of intoxication and the hypokalemia linked to these overdoses. Rather than a true potassium deficiency, the process appears to be an intracellular transfer of potassium.

It is well recognized that hydroxychloroquine can have major adverse effects, primarily cardiac arrhythmias, including the potential to lengthen the QTc interval. Additionally, these impacts might be amplified by the concurrent use of azithromycin or other medications. These two active substances can also lower blood sugar and harm the kidneys, liver, or nervous system. There have been reports of severe cardiac toxicity at blood levels of hydroxychloroquine ranging from 2.05 to 29.40 mcmol/l. In patients undergoing this medication for COVID-19, heart monitoring and plasma concentration monitoring are advised [3, 4].

Doxycycline and hydroxychloroquine are the usual treatments for Whipple's illness, a systemic infectious condition brought on by Tropheryma whipplei. The HCQ is given in this indication at the same dosage (600 mg daily) as in the suggested COVID-19 protocol. According to the literature, the target HCQ plasma levels are 1 +/- 0.2 ug/ml [5].

Kidney failure and hydroxychloroquine:

The kidneys are primarily responsible for excreting HCQ. Patients with renal insufficiency who are at risk of developing early cardiotoxicity receive special monitoring. According to the literature, dialysis does not considerably lower plasma concentrations, thus it was advised to use lower doses of HCQ [6,7], which varied depending on the type of dialysis and the glomerular filtration rate (table 1). The dose reductions shown in the tables are advised for systemic inflammatory diseases like lupus, where long-term use of HCQ at low dosages (200 mg) and in a single dose is advised in order to prevent cumulative retinal toxicity.

A 50% decrease in HCQ has been suggested due to the lack of expertise with dosage adjustment and to prevent early cardiac toxicity in individuals with renal failure. This patient's cardiac evaluation revealed no anomalies.

Renal Replacement Therapy	Daily Dose
CAPD	Non-dialysis. Dose for one GFR<10 mL/min
HD	Non-dialysis. Dose for one GFR<10 mL/min
HDF/highFlux	Dialysability not known. Dose for one GFR<10 mL/min
CAV/VVHD	Dialysability not known. Dose for one GFR=10–30 mL/min

Table II: Recommended daily dose of hydroxychloroquines according to glomerular filtration rate for the prevention of retinal toxicity. (GFR)[6]

GFR (mL/min)	Max daily dose of hydroxychloroquine
30–50	Maximum 75% of the dose
10–30	25–50% of the dose
<10	25– 50% of the dose– use with caution

Glomerular filtration rate (GFR), continuous arteriovenous/venovenous hemodialysate (CAV/VVHD), intermittent hemodialysate (HD), continuous ambulatory peritoneal dialysis (CAPD), and hemodialysate filtration (HDF).

Table III: Dose in Patients Receiving Renal Replacement Therapy [6]

Optimizing hydroxychloroquine for therapeutic purposes
The following procedures were followed in order to prepare 100 mg of hydroxychloroquine at the pharmacovigilance service for the therapeutic optimization unit:
I: Determining the active principle's entire mass
Total mass of the active ingredient = desired dosage * number of capsules to be made = 100 * 30 = 3000 mg
Being aware of:
The dosage * treatment duration = 3 * 10 = 30 equals the number of capsules to be prepared.
II. Specialization deconditioning
It involves figuring out how many pills or capsules need to be broken up or their contents emptied:
N Cp = number of desired units of dose * number of prepared capsules
N Cp, the starting medication dosage, is 100 * 30/200 = 15cp.
III. Modification of the diluent volume to be added
It is possible to calculate the volume of diluent to be added based on the desired capsule size. Each of the N ° 1 capsules requires 0.5 ml of diluent. 15ml of diluent is needed for 30 capsules.
IV: Trituration of the active component and diluent using a mortar V-Getting the capsule filler ready
VI-Capsule filling and ejection VIII-Labeling VII-Pillbox

Medicinal care
Prescription medication: 100 mg of hydrochloroquine gel three times a day for ten days; 500 mg of azithromycin on the first day and 250 mg for four days; and 1g of cefotaxime three times a day
• Ten days of 4000 IU of enoxaparin
After our team completed the pharmaceutical study, several drug-related issues were found:
1. Interaction between drugs:
It is not advised to use hydroxychloroquine and azithromycin together. The QT interval may be prolonged by

hydroxychloroquine. Theoretically, using azithromycin along with other medications that may lengthen the QT interval could have cumulative effects and raise the risk of ventricular arrhythmias, such as torsade de pointes and sudden death. Although the likelihood of a ventricular arrhythmia linked to QT prolongation is generally unpredictable, certain underlying risk factors, such as heart disease, congenital long QT syndrome, and electrolyte imbalances (e.g., hypokalemia, hypomagnesemia), may increase the risk. Furthermore, the type of medication used and its dosage determine how much QT prolongation is caused by it. Intervention using pharmaceuticals:
1. It is typically advised to avoid co-administration of hydroxychloroquine with other medications that can lengthen the QT interval. It is recommended that patients using hydroxychloroquine seek immediate medical attention. Pay close attention if they experience symptoms like lightheadedness, fainting, palpitations, irregular heartbeat, shortness of breath, or fainting that could be signs of torsades de pointes. [9].
2. Tisdale Score computation to estimate the likelihood of QT interval prolongation [10,11]: This score can be seen online at https://www.mdcalc.com/tisdale-risk-score-qt-prolongation#evidence
A low score is represented by the patient's computed score of 6: Low risk of QT interval prolongation; always keep in mind that a larger risk could arise depending on the pharmacokinetics, medication interactions, and clinical course. To check for symptoms of QT prolongation, we advise repeating the ECG 8 to 12 hours following the initiation of QT prolongation therapy. If any are seen, we recommend careful monitoring. Restore electrolyte imbalances and keep serum magnesium levels above 2.0 mg/d and blood potassium levels above 4.0 mEq/L.
2. Standard noncompliance or contraindication: Lovenox 4000 IU [12] daily for 10 days. Note: The following risk factors are well established for patients who are candidates for prophylaxis [13, 14, 15]: age, history of venous thromboembolic disease (VTE), acute infection, active malignancy, prolonged immobility, chronic heart failure, and insufficiency pulmonary illness.
Due to the patient's two risk factors (hospitalization and COVID-19 infection), thromboprophylaxis is required. -Explanation of the drug treatment issue: Due to the patient's inadequate renal end, low molecular weight heparin is not advised due to the increased risk of hemorrhage. Pharmacological intervention: Exchange/Substitution
If the patient's clearance is less than 15 ml/min (8 ml/min), HNF SC (calciparin, according to the establishment's registration) should be substituted. The suggested dosage for the thromboembolic risk is displayed in the table below:

Thromboembolic risk		
Weight	Low	Student
50-80 kg	5000 U 2 * / d	5000 U 3 * / d

Table IV: Recommended dosage depending on the thromboembolic risk **High risk:**
in the event of known thrombophilia, recent surgery, current malignancy, or a history of VTE. Nevertheless, we advise 5000U 2 * / d for our patient with a low thromboembolic risk.
1. Observations to be made on the HNF recommendation:

Kalemia, platelet count prior to therapy and two times per week while receiving treatment, When taking heparin for prevention, it is not advised to monitor liver balance prior to treatment or anti-Xa or TCA [16].
2. Cefotaxime (Claforan) 1G 3 * d for 10 days is an overdose or supra-therapeutic dosage [17]. Medicinal intervention: Modification of dosage
After a typical first dosage, maintenance dosages for individuals with a clearance of less than 10 milliliters per minute should be cut in half regular dosage without altering the interval between doses. Following an initial dose of 1G/3 * d, a dosage of 500 mg/3 * d is advised.
3. Observation to adhere to:
The liver is where hydroxychloroquine is processed, thus before beginning treatment, the liver balance must be assessed. Hydroxychloroquine builds up in the tissues as a result of liver failure, which is the same as an overdose [2].

Magnesemia: for the best cardiac monitoring, magnesemia must be performed in conjunction with kalemia [8].

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