The role of hydroxychloroquine sulfate in the geriatric patient with coronavirus disease 2019 (COVID-19). What is useful to know for the geriatrician?

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Abstract

The role of hydroxychroloquine (HCQ) sulfate as therapeutic option in coronavirus disease 2019 (COVID-19) patients aroused great interest and hope, so much so as to authorize several studies in the world. Despite the beneficial effects demonstrated *in vitro* and in some case-series, doubts remain about its clinical use, so that at present more than 20 different therapeutic study protocols have been proposed. Very recently, a protocol has been authorized by the Italian Medicines Agency (AIFA), in order to evaluate the efficacy of out-of-hospital treatment with HCQ in the reducing viral loads and need for hospitalization in symptomatic COVID-19 infected patients who are confined at home.

The article describes lights and shadows of HCQ therapy in the elderly and geriatric patients affected by COVID-19, and suggests that the geriatrician should use HCQ only after careful patient selection and be aware of its pharmacokinetic properties and adverse effects, before better-designed studies determine their benefit, if any, in treating COVID-19.

Introduction

Hydroxychloroquine (HCQ) sulfate is a synthetic drug belonging to the family of 4-aminoquinolines, first synthesized in 1946 by introducing a hydroxyl group at the end of the side chain of chloroquine (CQ) phosphate.[1] This modification proved to reduce CQ-related toxicity without substantially changing efficacy and pharmacokinetic properties. Indeed, following oral administration, as CQ also HCQ is almost completely absorbed (with an absorption rate 70-80%) and rapidly (within 2-4 h) distributed to different tissues (lung, among these), achieving the steady state in three weeks. Variability in the absorption can influence the achievement of the steady state and more in general HCQ pharmacokinetics (30-100%), as well as its efficacy. The terminal half-life is about 40 days, although a little amount of the drug is still found in the plasma, urine, and red blood cells several years after the administration. HCQ has predominantly a renal excretion.[2-6]

Hydroxychloroquine in clinical practice

The experience with patients affected by rheumatic diseases (in which HCQ has been used for several decades) highlighted that it can be considered a well-tolerated treatment rarely discontinued, even in elderly patients.[7-10] A dosage between 3 and 6 mg/bodyweight/day is considered effective, while dose exceeding the recommended maximum therapeutic dosage (*i.e.*, >6.5 mg/kg/day) is one of the most relevant risk factors for HCQ- adverse events (Table 1).

In obese individuals, the dosage must be assessed considering the patient's ideal body weight. Mostly reported adverse drug events (ADE) of HCQ include gastrointestinal symptoms and cutaneous manifestations.[11] However, these events disappear with dose reduction and rarely require the treatment withdrawal. More severe and rare adverse events include retinal, neuromuscular, and cardiac impairments.

Of the known medications reported to cause QT interval prolongation, HCQ is not commonly implicated. In 2017, during the *Malaria policy advisory committee meeting* organized by World Health Organization (WHO) no case of arrhythmic death was reported.[12] In 2018, .a systematic review article reported that the risk of cardiac adverse events (conduction disorders, among these) was not quantifiable because of the lack of randomized controlled trials and observational studies investigating this association.[13] Studies involving volunteers highlighted that the effect on QT interval prolongation is dependent on HCQ dose, with mean increases in QTc of 6.1 ms after a dose of 600 mg.[14]

In clinical practice, a baseline ECG is mandatory as well as it is prudent to correct electrolyte disorders and, where possible, avoid or minimize use of other drugs known to prolong the QT interval (see Table 1). The use of a risk score, such as the one proposed and validated by Tisdale *et al.,*[15] should be took into account, in order to avoid an additive toxicity. Finally, according to the American College of Cardiology suggestions, an ECG performed 2-3 h after the second dose of HCQ, and daily thereafter, should be acquired: if QTc increases by > 60 msec or absolute QTc > 500 msec (or > 530-550 msec if QRS > 120 msec), the dose of HCQ tshould be reduced).

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The possibility that HCQ can induce neuropsychiatric adverse events has been reported less frequently.[16-19] HCQ cross the blood–brain barrier and in the brain can have a tissue concentration 10–20 times higher than a plasma concentration.[20]

Hydroxychloroquine and severe acute respiratory syndrome-related coronavirus variant-2

In vitro studies reported that HCQ has potential to reduce the activity of severe acute respiratory syndrome-related coronavirus variant-2 (SARS-CoV-2), functioning at both the viral entry and post-entry stages of infection (Table 2).

Moreover, it is well know that HCQ can significantly decrease the production of pro-inflammatory cytokines (interleukin-6, among these), thereby counteracting the SARS-induced cytokine storm which strongly correlates with disease activity. Some clinical trials in patients with coronavirus disease 2019 (COVID-19) were then initiated, suggesting some positive results in terms of efficacy and safety. As know, all these studies had relevant bias and mixed results.[21-28]

According to literature review, however, very few data were available on elderly patients.

In particular, in an open-label non-randomized clinical trial published by Gautret *et al*. the mean age was of 45.1 years.[26] In an experimental study published by Yao *et al*., physiologically based pharmacokinetic (PBPK) models were applied to virtual sub-

Table 1. Risk factors of hydroxychloroquine-induced adverse events.

1)	Female gender
2)	Low body weight
3)	Alcohol intake
4)	Concomitant administration of CYP3A4 inhibitors (indinavir, nelfinavir, fluconazole, ketoconazole, itraconazole, amiodarone, verapamil, diltiazem, erythromicin, clarithomycin)
5)	Concomitant administration of drugs that may prolong QTc interval (clarythomycin, erythromycin, amiodarone, sotalol, domperidone, haloperidol, chlorpromazine…)
6)	Dose exceeding the maximum therapeutic dosage (>6.5 mg/kg/day)
7)	Hepatic cytochrome P450 enzyme 2D6 (CYP2D6) genetic variability, determining a *poor metabolizer* phenotype and an *ultrarapid metabolizer* phenotype
8)	Renal impairment
9)	Electrolyte disorders (mainly hypokalemia and hypo-magnesemia)

Table 2. Main effects of hydroxychloroquine against severe acute respiratory syndrome-related coronavirus variant-2 (*in vitro*).

-	Deficit in the glycosylation of ACE2 receptor.[21] ACE2 is expressed on surfactant-producing type 2 pneumocytes[14] and is considered the most important virus cell surface receptor;
-	Elevate the pH of intracellular organelles such as endosomes or endolysosomes essential for membrane fusion. In particular, this elevation blocks the transport of SARS-CoV-2 from endosomes to endolysosomes, stage necessary to release the viral genome.[22]
-	Post-transcriptional modification of viral proteins.[23]

jects aged between 20 to 50 years of age.[23] The data proposed by Yao *et al.* set the current standard of the recommended dosage of HCQ for the treatment of SARS-CoV-2, but the same article highlights that most probably these dosages should be not applied to the older patient.

With determination of 17 March 2020, the Italian Medicines Agency (AIFA) approved the use of HCQ and CQ only for treatment and not for prophylaxis of COVID-19. Very recently, the same AIFA approved a study protocol (Hydro-Stop-COVID19 Trial) that has the objective to evaluate the efficacy of out-of-hospital treatment with HCQ to reduce the viral loads and need for hospitalization in symptomatic SARS-CoV-2 infected patient who are confined at home (EudraCT number: 2020-001558-23). According to this trial, patients will receive HCQ 400 mg twice daily (loading dose) during the first day of treatment, followed by 200 mg twice daily for the next 6 days (total duration of treatment: 7 consecutive days). Patients aged 70 years or more, with known renal or liver impairment or heart diseases (coronary artery disease, dilated cardiomyopathy, hypertrophic cardiomyopathy) will not receive the 400 mg twice daily loading dose , but a 200 mg twice daily regimen for 7 consecutive days.

A few pharmacokinetic considerations

The most relevant and life-threatening manifestation of COVID-19 is acute respiratory distress syndrome. It has been documented that in animals, HCQ reaches lung levels of 200-700 times higher than those in the plasma,[29] and that in healthy volunteers, 6 mg/kg/day determined serum levels of 1.4 micromoles.[30] It has also been documented *in vitro* that the 50% cytotoxic concentrations values of HCQ were about 250 micromoles.[22] However, as for today, we do not know (if not empirically) after how long such concentrations are reached *in vivo*. In the older patient, this knowledge is near zero.

Hydroxychloroquine and coronavirus disease 2019 in elderly and geriatric patients

Age over 70 years and comorbid conditions (hypertension, respiratory morbidity, diabetes mellitus, heart diseases, among these) are relevant risk factors for sCOVID-19.

Polypharmacology that is frequent in older geriatric patients may increase the risk for drug-drug interactions, and the onset of HCQ-adverse events.

As already reported, new or worsening neuropsychiatric symptoms are possible adverse drug effects of treatment with HCQ. Indeed, given the speculative nature at present of HCQ in COVID-19 treatment, this drug should be avoided in patients with underlying mental illness, at least until more data are available. Moreover, some antipsychotics used in old patients (such as quetiapine, haloperidol, risperidone) may increase the risk for QT and QTc interval prolongation (see AIFA website).

Age-induced pharmacokinetic changes may create completely different scenarios in the older people compared to adult or young populations. Finally, some investigators suggested that the use of HCQ could worsen COVID-19, speculating that the inhibition of T-helper cell proliferation and interleukin-2 production or responsiveness induced by HCQ might raise the inflammatory response, negatively influencing patient outcomes.[31]

Conclusions

Despite a genuine enthusiasm expressed by some researchers for the potential of prescribing HCQ in the treatment of COVID-19, shadows seemed even more numerous than lights to the point that warnings are continuously increasing.[32,33]

Therefore, caution is advised especially in older and geriatric patients.

The geriatrician should use HCQ only after careful selection of patient and be aware of its pharmacokinetic properties and potential adverse effects, before better-designed studies may clearly demonstrate their benefit, if any, in treating COVID-19 in older patients.

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