Review Article

Optimizing the use of hydroxychloroquine in management of COVID-19given its pharmacological profile

Abstract

Hydroxychloroquine (HCQ) showed promising results in the management of COVID-19. We realized that there is no unified protocol for its use, but variable regimens and different protocols are applicable. Accordingly, its pharmacological profile was revised. The following practical guidelines were suggested to optimize its efficacy in the management of COVID-19. It should be used as early as possible. i.e., once the viral infection is confirmed or suspected. A loading dose is recommended to be given in 3-4 divided doses to minimize cardiac toxicity Maintenance daily dose (divided into two doses), should be continued until complete remission. Precautions, drug-interaction, contraindications, variable metabolic pathways in the special population should be considered. Special consideration ?confederation should be given to minimize and or manage HCQ cardiac toxicity

Keywords: hydroxychloroquine, COVID-19, Pharmacokinetic based regimen

Introduction

COVID-19 an overview

In December 2019, the authorities in Wuhan, Hubei Province, China, reported that there was an epidemic in progress, with a growing number of individuals suffering from pneumonia, which was linked to a new type of coronavirus, namely severe acute respiratory syndrome coronavirus 2 Over the next few weeks, the infection proliferated and extended outside China to more than 80 other countries. Experts list fever, tiredness and a sharp dry cough as the most common symptoms, but some infected individuals have also presented with aches and pains similar to flu, congestion and/or a runny nose, a sore throat or diarrhea. Approximately 80 percent of those who get the virus recover independently. However, some 16 percent of those who get COVID-19 have severe respiratory issues and become so ill they need hospitalization. On 11 February, a statement was put out by the Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses, stated that the virus had been officially termed a severe, acute respiratory syndrome coronavirus 2 (SARS-CoV-2), based on its phylogeny, taxonomy and recognized practice. The WHO subsequently named the illness Covid-19 It was suggested that the virus is originally hosted by bats, and then spread through the wild animals sold at the Huanan seafood market, before being further transmitted through human to human contact (Ciotti et al., 2020, Wu et al., 2020) (WHO 2020)

SARS-CoV-2 characteristics

COVID-19 is caused by β-coronavirus SARS-CoV-2.. (65-125nm), an enveloped viruses It has large (26-32 Kb) single-stranded, positive-sense RNA. It has about 80 % similarity to SARS-CoV, at a nucleotide level. The action of the spike protein (S protein) of C-19 interacts with Angiotensin-converting enzyme 2 (ACE2)receptor is the first1st step for entry into human cells invasion(ref). ACE2 is expressed on the surface of lung alveolar epithelial cells and enterocytes of the small intestine and other tissues(ref). It was considered highly infectious as it remains viable in aerosols for 3 hours, stable on plastic and stainless steel,

with up to 72 hours(ref). It is transmitted from human to human by infectious droplets, however, airborne transmission was suggested. The virus could be found on many surfaces like door handles and light switches. SARS-CoV-2 viral RNA has been found in nasopharyngeal swabs, faces and blood(ref). That direct contact, rather than airborne spread, is the main transmission route, The basic reproductive number, the so-called R0, of the virus is thought to be between ???

The mean incubation period is about 4-6 days with about 95% of individuals developing symptoms within 14 days after from infection, a mean serial interval of 6.6 days. They estimate that 95% of cases will develop symptoms within 16.1 days of symptom onset in their infector?? Risk factors include advanced age: for example the fatality rate 60-69 year-olds (CFR= 3.6%) Co-morbidities coexisting diabetes, cerebrovascular disease, chronic kidney disease chronic obstructive lung disease, male gender was not identified as a risk factor for in-hospital death, pregnancy was considered a risk factor(ref). There is currently no vaccine available against SARS-CoV-2 infection. (Cascella et al 2020) (Mackenzie and Smith, 2020, Rabaan et al., 2020)

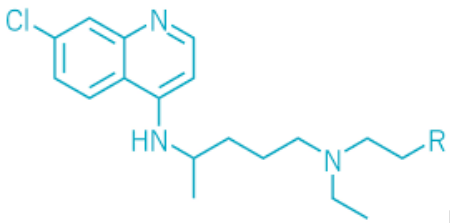
Pharmacotherapy of COVID 19 and drug repurposing

Numerous efforts have been paid to discover and evaluate the effectiveness of already known antivirals, immunotherapies, monoclonal antibodies, and vaccines in Covid-19(ref). repurposing existing therapeutic agents originally developed for other virus or infections, the disease seemed at present an optimal realistic approach for management of emerging pandemic, these drugs have known pharmacological profile(ref). Some of them showed efficacy *in vitro,*and careful revision of their pharmacodynamics have already been tested for their efficacy(ref). Pharmacodynamics (PD) and Pharmacokinetics (PK) suggest these drugs as a good candidate for clinical trials These agents can be classified according to their pharmacological targets. Moreover, some of these drugs have multiples targets andbenefits. A comprehensive list of these drugs can be found elsewhere. (Rabaan et al., 2020, Zhou et al., 2020b)Comprehensive reviews of clinical trials and brief pharmacological profile of selected drugs were assessed (Sanders et al., 2020)(Tobaiqy et al., 2020)

We will focus on one of the most promising repurposed drug,Hydroxychloroquine (HCQ), based on the effective results of preliminary studies(ref). It seemed to be effective in controlling SARS-CoV-2 infection. However, its use should be optimized given an understanding of its pharmacological characteristics and careful review of COVID-19 patients profile to ensure safety and efficacy.

HCQ as immunomodulator drug

HCQ is a less toxic metabolite that Chloroquine(CQ)(Gautret et al.) (Figure1),



Chloroquine, R = H
Hydroxychloroquine, R = OH

Fig. 1. Chemical structure of Hydroxychloroquine and Chloroquine

HCQ and CQ are considered to be immunomodulators rather than immunosuppressants(ref). In particular, HCQ can increase the intracellular pH and inhibits lysosomal activity in antigen-presenting cells (APCs), including plasmacytoid dendritic cells (pDCs) and B cells, so preventing antigen processing and major histocompatibility complex (MHC) class II-mediated autoantigen presentation to T cells. This process reduces T cell activation, differentiation, and expression of co-stimulatory proteins (e.g. CD154 on CD4!? T cells) and cytokines produced by T cells and B cells (e.g. IL-1, IL-6, and TNF).) Meanwhile, due to the altered pH of endosomes and interrupted binding between toll-like receptors (TLR7 and TLR9) and their RNA/DNA ligands, TLR signaling is suppressed by administration of HCQ(ref). In the cytoplasm, HCQ also interferes with the interaction between cytosolic DNA and the nucleic acid sensor cyclic GMP-AMP (cGAMP) synthase (cGAS). (As both TLR signaling and cGAS stimulation of interferon genes (the STING pathway) are impeded by HCQ, subsequent proinflammatory signaling activation and production of cytokines, such as type I interferons, IL-1 and TNF, are attenuated.

Such mechanisms give strong support to the hypothesis that HCQ is likely to confer an ability to suppress the CRS?, which is due to over activation of the immune system triggered by SARS-CoV-2 infection, through which progression of the disease from mild to severe might be attenuated. (Hughes, 2018).Evidence is emerging that COVID-19 is associated with an increased risk of thromboembolic disease,It is very infesting? that it is valuable for prophylaxis against lung thrombosis (Johnson and Charnley, 1979).

HCQ and SARS-CoV-2

Proposed mechanism

In addition to a role in immune modulation, HCQ and CQ inhibit receptor binding and membrane fusion, two key steps that are required for cell entry by coronaviruses. CQ has been shown to exert an antiviral effect during pre- and post-infection conditions by interfering with the glycosylation of angiotensin-converting enzyme 2 (ACE2) (the cellular receptor of SARS-CoV) and blocking virus fusion with the host cell (Figure 2, is not in text). Impaired terminal glycosylation of ACE2may reduces the binding efficiency between ACE2 on host cells and the SARS-CoV spike protein. Thus, the binding of the virus to the receptors on the cells is impeded and infection is consequently prevented. Once HCQ and CQ enter a cell they are both concentrated in organelles with low pH, such as endosomes, Golgi vesicles, and lysosomes. As the virus uses endosomes as a cellular entry mechanism, increasing the pH of endosomes through CQ treatment places a negative influence on the fusion process of viruses and endosomes. Lysosomal proteases activate the fusion process between host and viral membranes by cleaving coronavirus surface spike proteins. Increasing the pH of the lysosome prevents protease activity such that this fusion process is disrupted(Without the pH necessary for the endosome and lysosome to execute the cleavage function, replication of and infection by the coronavirus are blocked). Inhibition of SARS-CoV spread was observed in cells treated with CQ in non-infection stage, suggesting both prophylactic and therapeutic advantages of CQ in combating SARS-CoV Given that HCQ demonstrates similar molecular mechanisms to CQ, it is highly likely that HCQ will perform similarly in terms of early prevention and disease progression. Again, this requires careful *in vitro*and *in vivo*testing.(Sinha and Balayla, 2020)

*In vitro*efficacy of HCQ

HCQ showed activity against coronavirus and determined its EC50, which is slightly higher compared to Chloroquine (Gautret et al.) However, by contrast, Yao et al (1) found that HCQ was more potent against SARS-CoV-2 than CQ *in vitro*(EC50 of 0.72 μM and 5.47 μM, respectively. MOI = 0.01). Yao et al reported high selectivity of CQ for SARS-CoV-2 rather than host cells (Yao et al., 2020)

Clinical Trials & debates about HCQ efficacy and safety

Few promising clinical trials demonstrated the effectiveness of both CQ and HCQ in the early management of COVID-19. First clinical trial in China, (about 100 patients with COVID 19), brief results indicated that chloroquine phosphate resulted in clinical improvement of viral pneumonia and marked reduction in the duration of illness, no serious adverse effects were reported. A limited non-randomized clinical trial (36 patients diagnosed with SARS-CoV-2). treatment group, received HCQ 200mg three times a day for ten days. The control group received usual care. (few patients in the treatment group also received azithromycin). The authors suggested that these empirical findings suggested the promising effectiveness of HCQ and a potential synergistic effect with azithromycin. (Gautret et al., 2020a)

A recent meta-analysis concluded that HCQ is a promising treatment for COVID-19 patients, good safety profile, clinical improvement based on radiological findings but more data still needed to provide the final conclusion.(Sarma et al., 2020). Many health authorities consider HCQ to be investigated under clinical trial for management of COVID 19 (Miki et al 2020)

Criticism and debates

Some authors provided criticism for these studies, and focused on considerable limitations, regarding statistical power or insufficient data, lacks medium and long-term follow-up among other, (Molina et al., 2020)

The pharmacokinetic (PK) profile of HCQ

HCQ has large Vd and long t, it is administered as sulfate, and has a bioavailability of 0.7. Renal clearance is an important clinical consideration, especially in patient with renal failure. Peak plasma levels of hydroxychloroquine were seen in about 3 to 4 hours. The absorption half-life was approximately 3 to 4 hours and the terminal half-life ranged from 40 to 50 days. The long half-life can be attributed to extensive tissue uptake Reference ID: 4047416 rather than through decreased excretion.

HCQ binds strongly to melanin and can deposit in melanin-containing tissue such as the skin and the eyes, which might explain certain tissue-specific mechanism such as retinopathy. HCQ is a substrate for CYP 450 and can interfere with several drugs metabolized by these

enzymes so screening for drug interaction should be manipulated to ensure its optimal use in the management of COVID-19, (Evan et al 2020) (hydroxychloroquine drug com 2020) (hydroxychloroquine FDA 2020)

A physiological pharmacokinetic model was recently developed to support whether HCQ lung concentration levels will be sufficiently high enough to treat SAR-COV2- infection or not.In the final PBPK model they simulate HCQ lung concentrations with multiple dosing regimens and recommended that a dosing regimen that they believed (400mg BID for 1 day followed by 200 mg BID for 4 days, besides starting this regimen as early as possible will provide sufficient HCQ lung concentrations without reaching HCQ unsafe levels and improve clinical outcome. (Arnold and Buckner, 2020b) This approach was suggested to enhance our confidence in the utility of modeling to optimize HCQ use (Molina et al., 2020)

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Side Effects of CQ/HCQ an overview

The safety profile of CQ/HCQ is well documented. These include GIT side effects with HCQ intake Retinal toxicity associated with prolonged use of CQ and HCQ or overdose.Rarely CQ may produce cardiomyopathy and arrhythmia. There is a list of precautions and contraindications of both drugs, for example, CQ is contraindicated in patients with porphyria (Both drugs should be used cautiously in patients with liver or renal failure), Clinician should also consider the reported possibility of the liver and renal impairment, induced by COVID-19. (hydroxychloroquine Monograph 2020)

Focusing on particular adverseeffects of HCQ likely relevant with a short course:

1. Cardiotoxicity of HCQ:

It has been noticed that HCQ can lead to QT prolongation and torsade de pointes (Tsp.) development in susceptible individuals. However, there is no strong correlation between the risk of Tsp. development and drug- prolongation of QT intervals by drugs since not all patients with drug-induced QT prolongation will develop Tsp. However, despite this cardiotoxic effect HCQ is rare, co-prescription of azithromycin in Covid-19 could amplify this risk with HCQ(Cascella M, 2020). Therefore, ECG monitoring is recommended as essential tools, and QT interval evaluation to all hospitalized COVID-19 patients before starting HCQ is crucial to avoid the possible cardiotoxicity(Cascella M, 2020). Similarly, Chronic hydroxychloroquine use was associated with QT prolongation and refractory ventricular arrhythmia as reported. Additionally, cardiomyopathies were induced with HCQ

and should be considered in patients receiving these medications for Covid-19 and such cardiotoxic effects may explain muscle weakness or cardiac symptoms

On the other hand, it has been shown that HCQ acts as a bradycardic agent in SAN cells, in atrial preparations, and *in vivo* . HCQ slows the rate of spontaneous action potential firing in the SAN through multichannel inhibition, including that. This effect may be beneficial in Covid-19 patients with past-history of sinus tachycardia or angina pectoris. On the bases of all the previous observations, these drugs should be administered under close medical supervision, with monitoring for cardiotoxic side effects particularly QTc interval. Myocarditis, pericarditis, and cardiomyopathy in addition to potassium imbalance may increase the risk for arrhythmias-associated with HCQ particularly in elderly patients with Covid-19. In a very recent unpublished study, unfortunately, the following statement has been written: "Worryingly, significant risks are identified for combination users of HCQ+Azithromycin even in the short-term as proposed for COVID19 management, with a 15-20% increased risk of angina/chest pain and heart failure, and a two-fold risk of cardiovascular mortality in the first month of treatment" (Derek Lowe, April 11, 2020: The Latest Hydroxychloroquine Data, Drug in the Pipeline).

Suggested Cardiac monitoring of Covid 19 patients on HCQ

Additionally, the baseline ECG allows for documentation of the QT (and corrected QTc) interval. Importantly, QTc will need to be monitored as chloroquine therapy can cause QT prolongation especially if used with azithromycin.

Overall, the average QTc in healthy persons after puberty is 420±20 milliseconds. In general, the 99th percentile QTc values are 470 milliseconds in postpubertal males and 480 milliseconds in postpubertal females

In general, patients with the following QTc intervals are at low risk for significant QT prolongation and polymorphic VT:

- QTc <460 milliseconds in prepubertal males/females
- QTc <470 milliseconds in postpubertal males
- QTc <480 milliseconds in postpubertal females

A QTc >500 milliseconds is considered highly abnormal for both men and women.

In such patients, efforts should be made to correct any contributing electrolyte abnormalities (eg, hypocalcemia, hypokalaemia, and/or hypomagnesemia), with goal potassium of close to 5 mEq/L.

Even in those with a normal QT interval, there should be a review and discontinuation of any QT-prolonging medications that may not be essential to the immediate care of the patient (e.g., proton pump inhibitors, etc) (Molina et al., 2020)

2. Ocular toxicity of HCQ:

Ocular side effects of HCQ include retinal toxicity (which can lead to permanent visual impairment) and deposition of the drug in the cornea. HCQ appears to be considerably less toxic to the retina than chloroquine, possibly because chloroquine crosses the blood-retinal barrier more easily. HCQ ocular toxicity depends critically on daily dosage and duration of use, as well as other risk factors. With attention to dosage and other factors, and with proper screening for early signs of toxicity. Riskfactors includea daily dose of hydroxychloroquine >5.0 mg/kg (body weight), severe renal impairment, concomitant use of tamoxifen and duration of use >5 years (Yam and Kwok, 2006, Melles and Marmor, 2014)

We suggest thatidentifying abnormalities with screenings and examination before the patient's visual complaints is essential when HCQ is suggested to be used in Covid-19especially in the elderly.

3. Hypoglycemic effects:

HCQ induced hypoglycemia is well documented in the literature (Salman et al 2020) (El-Solia et al., 2018), Interestingly this hypoglycaemic effect was suggested to be of clinical value as add on the drug to control T2DM in patients not adequately controlled on multiple medications (Wolfe and Cordero, 1985)Concerning the use of HCQ in COVID-19 patients, careful follow up of glucose level should be implemented, In case of diabetic patients. antidiabetic drug regimen should be tailored and individualized to each patient to avoid serious hypoglycemia,

4. HCQ and Pregnancy:

Pregnant women have changes in their bodies that may increase their risk of some infections and have a higher risk of severe illness when infected with viruses as COVID-19. Safety of hydroxychloroquine in pregnant patients with connective tissue diseases has been studied on one hundred thirty-three cases compared with a control group. There was no statistical difference between HCQ and control groups and the authors considered HCQ is a safe drug(Costedoat-Chalumeau et al., 2005) However, its safety in pregnant females with Covid-19 so far is not clear and needs to be clarified. Chloroquine was also showed no appreciable teratogenic effect in pregnant women, administered the drug for chemoprophylaxis of

malaria. (Wolfe and Cordero, 1985). Fortunately, in Covid-19, HCQ is used for a short period ofa low dose for prophylaxis. It is likely if no other risk factors in pregnant womenthe benefit of using HCQ in management of COVID 19 outweigh its low potential risk of teratogenicity

5. HCQ and elderly population:

There are no studies that have been done on this population of older Covid-19 patients. However, as a consequence of aging, it has been established from basic pharmacological sciences that the potential harms of medications in aging populations increased as a result of diminished elimination pathways. Therefore, great cautions must be considered when HCQ is given to elderly populations with Covid-19 and suspicion of toxicity is expected. Accordingly, patient monitoring is essential.

6. HCQ and breastfeeding:

Infants exposed to hydroxychloroquine during breastfeeding receive only small amounts of the drug in breastmilk. A recent study in chinese women taking HCQ for connective tissue disease indicated that HCQ is not likely to be harmful to infants on breastfeeding (Peng et al., 2019). Concerning Covid-19, a low dose for prophylaxis not likely to be harmful to infants >1 month. For confirmed cases, the baby is thought to be isolated away from his mother In neonates, in theoretical we are warry about HCQ potentially displace bilirubin and result in the development of kernicterus. Low metabolic capacity, potential accumulation to induce cardiac toxicity.

Conclusion

Clinical trials still going on to provide a final solid conclusion regarding the efficacy and safety of HCQ in the management of COVID -19. However, its pharmacology (multiple actions) suggests it stands as an important drug to consider . We provided general guidelines to enhance the benefit to risk ratio. Using the drug in the early phase of infection, use a loading dose (200mg QID). Followed by adequate MD (200 mg BD). Dividing the doses is intended to reduce peak level which likely associated with cardiacarrhythmia. The regimen should be for an adequate period(maybe up to 7-10 days). The drug can be considered for prophylaxis. We believe benefits outweigh the risk in pregnant women . Optimal cardiac, sugar level, electrolyte monitoring is mandatory especially in elderly, diabetics, cardiovascular disorders. Interaction with other medications has to be considered. The clinical pharmacist has a major role in all these issues

Addional bioblography

(Alia and Grant-Kels, 2020, Arnold and Buckner, 2020a, Bell et al., 2020, Brufsky, 2020, Colson et al., 2020, Costanzo et al., 2020, Falcao et al., 2020, Fantini et al., 2020, Ferner and Aronson, 2020, Gao and Hu, 2020, Garcia-Cremades et al., 2020, Gautret et al., 2020a, Gautret et al., 2020b, Gbinigie and Frie, 2020, Graef et al., 2020, Guastalegname and Vallone, 2020, Heldwein and Calado, 2020, Jakhar and Kaur, 2020, Joob and Wiwanitkit, 2020, Juurlink, 2020, Kapoor et al., 2020, Keshtkar-Jahromi and Bavari, 2020, Kim et al., 2020, Kutlu and Metin, 2020, Lenzer, 2020, Liu et al., 2020, Mack, 2020, Mahase, 2020, Marmor, 2020, Megarbane, 2020, Moiseev et al., 2020, Molina et al., 2020, Patri and Fabbrocini, 2020, Pereira, 2020, Perinel et al., 2020, Peschken, 2020, Picot et al., 2020, Principi and Esposito, 2020, Rathi et al., 2020, Sahraei et al., 2020, Sarma et al., 2020, Schwartz and Janniger, 2020, Scuccimarri et al., 2020, Shah et al., 2020, Singh et al., 2020, Sinha and Balayla, 2020, Taccone et al., 2020, Xie et al., 2020, Yao et al., 2020, Yazdany and Kim, 2020, Zhang and Zhong, 2020, Zhou et al., 2020a)

disclaimer

This article is intended for education and research purposes only. It is not a substitute nor aimed to change recommendations provided by national or international guidelines for the management of COVID-19

Information are provided to illustrate concepts but not aimed to be used for any kind of interventions in clinical Authors tried to do their best but does not guarantee, the accuracy, reliability, completeness of information provided in this review They are not

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