Chloroquine and Hydroxychloroquine in COVID-19: Practice Implications for Healthcare Professionals

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ABSTRACT

Chloroquine (CQ) and its derivatives such as hydroxychloroquine (HCQ) remain mainstay of therapy for malaria. These drugs are also approved for certain autoimmune diseases including systemic lupus erythematosus. The antiviral activities of these drugs and their mechanisms have been studied *in vitro* previously against various viruses including severe acute respiratory syndrome coronavirus (SARS-CoV). During the current coronavirus disease 2019 (COVID-19) pandemic, *in vivo* and *in vitro* investigations of these drugs have demonstrated potential against severe acute respiratory syndrome coronavirus 2 (SARS--CoV-2). The authors used the keywords to find the relevant studies, like COVID-19, SARS-CoV-2, pandemic, complications, repositioning, toxicity, overdose, treatment plan, implication strategies, prevention, chloroquine, hydroxychloroquine, clinical trials, drug interactions, and practices advice, etc., in Pubmed and Google Scholar. This review aims to provide a detailed insight of practice implications related to these drugs, which would aid healthcare professionals to ensure the safe use of these drugs during the management of patients with COVID-19 disease.

Key Words: *Chloroquine, Hydroxychloroquine, COVID-19, SARS-CoV-2, Practice implications.*

How to cite this article: Mallhi TH, Ahmad A, Butt MH, Misbah S, Khan YH, Alotaibi NH. Chloroquine and Hydroxychloroquine in COVID-19: Practice Implications for Healthcare Professionals. *J Coll Physicians Surg Pak* 2020; **30(JCPSPCR)**:CR124-CR128.

INTRODUCTION

The whole world is going through unprecedented crisis due to coronavirus disease 2019 (COVID-19) pandemic and there is a dire need to discover therapeutic and prophylactic drugs to combat the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Drug repurposing, also known as drug repositioning, re-tasking or re-profiling, is considered as the most effective strategy during the current pandemic until specific treatments are made available. This strategy revolves around identifying new uses for approved or investigational drugs that are outside of the scope of the original medical indication. The primary benefit of this strategy over drug discovery is the use of de-risked compounds, with potentially lower overall development costs and shorter development timelines.[1] Given the sharp rise in COVID-19 cases and low pace of new drug discovery and development, the drug repurposing is the need of the time.

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Received: June 18, 2020; Revised: June 19, 2020;
Accepted: July 21, 2020
DOI: https://doi.org/10.29271/jcpsp.2020.JCPSPCR.CR124

Recently, Food and Drug Administration (FDA) approved the use of chloroquine (CQ) and its derivative hydroxychloroquine (HCQ) for the management of COVID-19 patients, following positive preliminary results from *in vitro* and *in vivo* investigations. Though these medications have established safety profiles; but numerous studies have also demonstrated the adverse events during the use. The current manuscript underscores important practice implications which should be considered while managing COVID-19 patients with CQ or HCQ.

CQ was first discovered in 1934 and its therapeutic value was confirmed after ten years following various investigations from six countries. CQ and its derivative HCQ, are well established antimalarial agents.[2] In 1947, CQ was approved for the prophylaxis of malaria. It was later added to the World Health Organization (WHO) model list of essential medicines. Being anti-parasitic agents, CQ and HCQ are FDA approved drugs for the prophylaxis and treatment of uncomplicated and CQ-sensitive malaria; and for the treatment of extra-intestinal amebiasis. Both drugs are also well known for their anti-inflammatory and immunomodulatory effects. [3] Keeping in view their antiviral potential, these drugs have been recently repurposed for the treatment and prophylaxis of COVID-19.[4] It must be noted that both drugs are used as potential treatment for wide spectrum of diseases, including both infectious and non-infectious diseases including the wide range of cancers,[5] systemic lupus erythematosus, primary progressive multiple sclerosis, systemic scle-

rosis, rheumatoid arthritis, Whipple's disease, Q fever, and several viral and fungal infections.[6]

CQ and HCQ are weak bases having characteristic-wide volume of distribution and are known to accumulate in the intracellular compartments of human cells such as lysosomes, endosomes and Golgi vesicles. This leads to a number of effects, specifically increasing the pH of lysosomes and endosomes.[7] The mechanism of action against SARS-CoV-2 is under continuous study. The mechanism that is believed to result in inhibition of SARS--CoV-2 involves the entry of non-protonated CQ inside the cell, accumulating in the acidic compartments.[8] The increasing pH might result in expansion and vacuolisation causing impairment of lysosomal and endosomal function and maturation, inhibiting the antigen presentation through the lysosomal pathway.[9] This potentially reduces the post-transcriptional modification of proteins, enzyme release, receptors recycling, cellular signalling pathways activation, and cell membrane repair.[10] Additional mechanisms include inhibition of ACE2 receptors, acidification at cell membrane surface (causing inhibition of viral fusion) and cytokine release immunomodulation.[11-13]

CQ and its derivatives have previously demonstrated i*n vitro* antiviral activity against severe acute respiratory syndrome associated coronavirus (SARS-CoV) and COVID-19 disease caused by novel SARS-CoV-2.[8,11,12] Though CQ has demonstrated i*n vitro* activity against various RNA viruses, but randomised control trials in dengue and chikungunya failed to demonstrate its effectiveness.[14] According to an experimental study, CQ was used in the treatment of 100 COVID-19 patients, and it showed clinical improvements with improved radiological image findings, reduced progression, and increased viral clearance.[15] Another open-label and non-randomised trial in France, consisting of 36 COVID-19 patients (20 received HCQ and 16 received control), reported that treatment with HCQ (200 mg, PO, 8-hourly regimen) resulted in enhanced viral clearance as compared to the control group.

This study also reported that addition of azithromycin to the regimen in six patients resulted in better viral clearance compared to patients receiving HCQ alone.[16] Different clinical trials have been conducted among patients with age ranging from 18 to 65 years in which varying dose regimens were used among patients (Table I).[17-20]

Safety profile of CQ and HCQ:

When taken according to prescription, CQ and its derivatives have established safety profile. However, higher doses have been reported to cause severe adverse effects. Most severe of which are retinal toxicity, diplopia, reduced visual acuity and bilateral loss of vision.[21] Some studies have also linked high dose administration with severe psychiatric issues, such as hallucinations, paranoia, and suicidal thoughts.[22] Dermatological effects related to CQ administration include photosensitivity and pruritus. Typically, retinopathy manifests with failure to focus between near and far objects. Neurological effects might include seizures, hallucinations, and paranoia. Intramuscular administration of CQ has been linked with hypotension that might potentially be lethal.[23] FDA has advised that CQ and HCQ are linked to cardiac events as they increase QT interval and limit the use of these drugs for clinical trials and for those patients who cannot participate in the trials.[24] CQ and HCQ may interact with many other drugs having potential to cause ECG abnormalities, which can result in augmented QT prolongation. These interactions must be controlled while managing the patients with COVID-19. CQ also induces haemolysis and causes problems in certain group of people, if used prophylactically in large populations.[25] Table II describes the list of potential interactions along with their severity level, mechanism, and management. Moreover, the use of CQ and HCQ may pose adverse outcomes in certain pre-existing conditions.[25] Table III demonstrates the interaction of these drugs with various diseases along with severity and monitoring strategies.

Drug dosing and adverse drug profile of CQ and HCQ:

The dosing of CQ should ideally be based on the body height and weight. In prophylaxis of malarial infection, 5 mg per kg of the body weight and not more than 500 mg once per week, is an appropriate regimen of dosing and HCQ (800 mg) twice daily for five days will be recommended dose for the COVID-19 patients.[23]

Although toxicity of CQ is rare, but it has been reported in unusually high dose ingestions or chronic intravenous administration. Retinal manifestations are most common following the poisoning of CQ. CQ toxicity is not easy to manage, but can be treated with epinephrine and diazepam along with mechanical ventilation. However, these treatment modalities require further investigations.[23]

Overdose of CQ and HCQ is extremely toxic and share common manifestations as for tricyclic antidepressants poisoning. Their intoxication leads to sudden onset of seizures and coma, cardiovascular collapse with sodium and potassium channels' inhibition, which results in wide QRS and prolonged QT interval, respectively and intracellular shifting induced hypokalaemia. High dose ingestion can be managed with non-specific measures such as activated charcoal and gastric emptying. However, intravenous vasopressors and benzodiazepines are also used for symptomatic patients. Sodium bicarbonate or hypertonic saline can be used to correct arrhythmias and QRS widening. It must be noted that every case of overdose should be reported to drug and poison control centre immediately.[26]

It is pertinent to mention that poisoned patients must be considered for ICU admissions. Monitoring of the vital signs including blood pressure, electrocardiogram (ECG) and respiration is of utmost importance. Biochemical investigations must focus on serum electrolytes, particularly the potassium levels. Other supportive measures include cardiac resuscitation and artificial ventilation. Since dosing of CQ and HCQ varies across studies, clinicians must monitor the patients for toxidromes, particularly among those with underlying cardiovascular disorders.

Table I: Recommended dose and duration of chloroquine (CQ) and hydroxychloroquine (HCQ) in COVID-19.

Recommended dose	Duration of use	Special comments	Reference
CQ 300 mg BID CQP 500mg BID	Maximum 10 days	For treatment	[17]
CQP 500 mg BID For body weight <50 kg use CQP 500 mg per day	7 days	50 mg/kg is a fatal dose, No dosing recommendation for Children	[18]
CQ 600 mg stat + 300 mg after 12 hours on day 1, followed by 300 mg BID from day 2-5	Maximum 5 days	For treatment	[19]
HCQ 200 mg daily CQP 500 mg BID	10 days	For Treatment	[19]
CQP 500 mg BID for 10 days	Minimum 5 days	Discontinue or Reduce one's daily if GI symptoms occurs	[20]
HCQ 200 mg TID	10 days	Using HCQ with Azithromycin inhibits 100% viral load in 6 days	[16]
HCQ 400 mg BID on day 1 and on day 2-5 use 200 mg BID	5 days	HCQ effective than CQP	[12]
CQ: Chloroquine, CQP: Chloroquine phosphate, HCQ: Hydroxychloroquine, BID: Two times a day, TID: Three times a day.			

Table II: Drug-drug interaction; its mechanism, severity level and management strategies.

Drug	Interacting drug	Mechanism	Management	Severity level
CQ, HCQ	Amiodarone	Prolongs the QT interval	Avoid co-administration	Major
CQ, HCQ	Quinidine	Prolongs the QT interval	Avoid co-administration	Major
CQ, HCQ	Sotalol	Prolongs the QT interval	Avoid co-administration	Major
CQ, HCQ	Procainamide	Prolongs the QT interval	Avoid co-administration	Major
CQ, HCQ	Vemurafenib	Prolongs the QT interval	Avoid co-administration	Major
CQ, HCQ	Vigabatrin	Prolongs the QT interval	Avoid co-administration	Major
CQ, HCQ	Citalopram	Prolongs the QT interval	Avoid co-administration	Major
CQ, HCQ	Escitalopram	Prolongs the QT interval	Avoid co-administration	Major
CQ, HCQ	Gatifloxacin	Prolongs the QT interval	Avoid co-administration	Major
CQ, HCQ	Moxifloxacin	Prolongs the QT interval	Avoid co-administration	Major
CQ	Ribociclib	↑ risk of an irregular heart rhythm	Avoid co-administration	Major
CQ	Tramadol	Tramadol rarely cause seizures	Use with caution	Major
CQ	Bupropion	↑ risk of seizures especially elderly people	Extreme caution; dose adjustment carefully.	Major
CQ, HCQ	Propafenone	Prolongs the QT interval	Avoid co-administration	Moderate
CQ, HCQ	Venlafaxine	Prolongs the QT interval	Clinical monitoring is recommended	Moderate
CQ, HCQ	Duloxetine	CQ ↑ the blood levels and effects of Duloxetine.	Need dose adjustment	Moderate
CQ, HCQ	Antacids	↓ Absorption of CQ and HCQ by magnesium trisilicate.	Separate dosage with 2-3 hours interval	Moderate
CQ, HCQ	Kaolin	↓ CQ levels absorption	Separate doses by at least 4 hours	Moderate
CQ, HCQ	Cimetidine	↓ Metabolism and clearance of CQ and HCQ.	Use alternative or take at least after 2 hours	Moderate
CQ, HCQ	Penicillamine	CQ ↑ peak plasma levels of penicillamine	Monitor acute toxicity	Moderate
CQ, HCQ	Ciprofloxacin	CQ modestly ↓ ciprofloxacin levels	Avoid co-administration	Moderate
CQ, HCQ	Atomoxetine	cause prolongation of the QT interval	Clinical monitoring is recommended	Moderate
CQ, HCQ	Digoxin	↑ levels of digoxin	Monitor digoxin levels; dose adjustment	Moderate
CQ	Ampicillin	CQ ↓ the absorption of ampicillin	Should be administered at least 2 hours apart	Moderate
CQ, HCQ	Methotrexate	CQ caused a moderate ↓ and HCQ caused a minor ↑ in the AUC of methotrexate.	Monitoring closely for reduced efficacy and adjust the dose.	Minor
CQ, HCQ	Metoprolol	CQ and HCQ ↑ the blood levels of metoprolol.	Consider use of alternative	Minor
CQ, HCQ	Ciclosporin	↑ plasma conc. of ciclosporin and impair renal function	Monitor renal function weekly	Unknown
CQ	CP	↑ plasma level and therapeutic efficacy of CQ	Monitor regularly cardiac toxicity	Unknown
HCQ	Porfimer	↑ risk of photosensitity reactions	Avoid exposure of skin and eyes to direct sunlight	Unknown
HCQ	Insulin	HCQ inhibit insulin degradation	Check blood sugar level and reduce daily dose of insulin	Unknown
HCQ	GC	↓ insulin clearance and degradation rate.	Check blood sugar level and adjust dose of GC	Unknown
HCQ	Rifampicin	↑ the metabolism and clearance of the HCQ	Avoid use of HCQ	Unknown
References: [25]. CP: Chlorpheniramine, GC: Glibenclamide, CQ: Chloroquine, HCQ: Hydroxychloroquine, AUC: Area under curve, ↑; Increases, ↓; Decreases, Major: Highly clinically significant, Moderate: Moderately clinically significant, Minor: Minimally clinically significant, Unknown: No severity level information available.				

Table III: Drug-disease interactions and their monitoring strategies.

Disease	Severity level	Monitoring strategies
Ocular toxicity	Major	Use if potential benefits are anticipated to the outweigh risks
Porphyria	Major	Should not be used in these patients unless the potential benefits are anticipated to outweigh risks.
Bone marrow suppression	Moderate	Administer cautiously. A complete blood count should be performed periodically in patients on prolonged therapy. Discontinuance of drug, If any severe blood disorder appears.
Ototoxicity	Moderate	Should be administered cautiously.
Seizures	Moderate	Should be administered cautiously.
Hepatotoxicity	Moderate	Periodic evaluation of hepatic function should be performed during prolonged therapy.
Heart disease	Moderate	Therapy should be monitored.
Psoriasis	Moderate	Should not be used unless the potential benefits are anticipated to outweigh the risks.
Reference.[25]		

The use of CQ and HCQ in children and pregnant women is proved to be safe. These drugs have few but highly fatal

contraindications. Death has been reported with the use of CQ in patients with porphyria cutaneous tarda. The use of these drugs is contraindicated in patients with retinal or vision changes, except in case of acute malaria. The hypersensitivity and allergic reactions are also reported in the literature. CQ is also contraindicated in patients with the history of HCQ hypersensitivity reactions.[23, 27]

Risks of self-medication:

It must be noted that uncontrolled amplified dissemination of news or information by the lay press, electronic and social media may trigger self-medication of drugs among general community. It is pertinent to mention that every news channel or agency is efficiently engaged to break any new findings or studies related to the treatment and prevention of COVID-19. Such news reports may influence the people who are searching for appropriate measures to save themselves from the virus. Though these drugs have established safety profiles but their potential to pose substantial adverse effects cannot be disregarded. Any sort of self-medication during the current pandemic may aggravate the ongoing health crises, for which none of the country is readily prepared. We believe that restricted and careful media announcements, active involvements of pharmacists and drug regulators with positive support from the national health authorities will mitigate the potential risks of self-medication and subsequent drug shortage and price hike during the current pandemic.

Practice advice and precautions:

The safety of CQ and its derivatives has been well studied and established with its use over decades.[28] However, several precautionary measures should be taken during the management of COVID-19 patients. These measures include blood testing to ascertain anaemia, leukopenia, thrombocytopenia, serum electrolyte disturbances, renal and hepatic dysfunction, ECG to assess QT prolongation and arrhythmias and physical examinations to observe the visual or mental disturbances. Antidepressants, antiarrhythmics and drugs having potential to prolong QT interval (quinolones, ondansetron, macrolides) must be avoided with CQ and HCQ.[20] *In vivo* investigations have indicated no harms to foetus among pregnant women.[29] Risks of long-term use include retinopathy, vascular myopathy, cardiac conduction disturbances, restrictive cardiomyopathy, and neuropathy.[30] In case of COVID-19, long-term risks are not relevant unless the drugs are used in prophylaxis for extended time.[26] Last, but not the least, physicians should report any unusual effect of these drugs during the management of COVID-19 patients.

Practice implications:

Since WHO has resumed CQ and HCQ trials, it is imperative to provide necessary information regarding implications of their use. FDA has approved CQ and HCQ for the COVID-19 patients who cannot participate in the clinical trials. These medications have established safety profiles; but numerous studies have also demonstrated the adverse events during the use. During the current COVID-19 turmoil, discovery of specific antivirals is the need of the hour. This review highlights the important practice implications which could ensure the safe and effective use of these drugs in COVID-19.

CONCLUSION

A number of research studies have evaluated the effectiveness of CQ and HCQ in COVID-19. However, clinicians must consider all precautionary measures to ensure the safe and effective use of these drugs during the management of COVID-19 patients. The use of these drugs must be subjected to institutional or national guidelines and should adhere to evidence-based medicine.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

THM, AA and MHB: Conception or design of the work.
MHB, AA, SM and YHK: Drafted the work.
THM, YHK and NHA: Revised the manuscript critically for important intellectual content.
THM, AA, MHB, SM, YHK and NHA: Provided approval for publication of the content.

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