REVIEW ARTICLE

A review on the pharmacokinetic properties and toxicity considerations for chloroquine and hydroxychloroquine to potentially treat coronavirus patients

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Abstract

The SARS-CoV-2 virus, caused a novel emerged coronavirus disease, is growing rapidly worldwide. Few studies have evaluated the efficacy and safety of Chloroquine (CQ), an old antimalarial drug, and Hydroxychloroquine (HCQ) in the treatment of COVID-19 infection. HCQ is derived from CQ by adding a hydroxyl group into it and is a less toxic derivative of CQ for the treatment of COVID-19 infection because it is more soluble. This article summarizes pharmacokinetic properties and toxicity considerations for CQ and HCQ, drug interactions, and their potential efficacy against COVID-19. The authors also look at the biochemistry changes and clinical uses of CQ and HCQ, and supportive treatments following toxicity occurs. It was believed that CQ and HCQ may provide few benefits to COVID-19 patients. A number of factors should be considered to keep the drug safe, such as dose, in vivo animal toxicological findings, and gathering of metabolites in plasma and/or tissues. The main conclusion of this review is that CQ and HCQ with considered to their ADMET properties has major shortcomings and fully irresponsible.

Keywords Chloroquine · COVID-19 · Metabolism · Toxicity

Introduction

In late 2019, the first case of a novel pneumonia caused by a previously unknown pathogen was appeared in China [1]. On 12 January 2020, the World Health Organization (WHO) named this virus as SARS-CoV-2 as the cause of 2019 novel coronavirus infectious disease (COVID-19) [2, 3]. COVID-19 could be dangerous, especially for the old persons [4].

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According to the WHO, as of August, 16, 2020, there are 21,294,845 confirmed cases and 761,779 deaths [5]. The virus binds to epithelial cells of the nasal cavity and replicates, and ACE2 is the main receptor for COVID-19 [6]. The number of CD8 + and CD4 + T cells in the peripheral blood of COVID-19-infected patients is significantly decreased. Acute respiratory distress syndrome (ARDS) is the common immunopathological event and main death cause of COVID-19 [7, 8]. Cytokine storm is one of the main mechanisms for ARDS, which cause multiple organ failure, and finally lead to death in severe cases of multiple organ COVID-19 infection [7].

In 2003, at the time of the SARS-associated coronavirus epidemic [9], several drugs had been evaluated to assess their effectiveness on this virus; one of them is chloroquine (CQ) [10]. These findings have been forgotten, because of the disappearance of SARS for reasons that are neither clear nor explained [11]. Also, studies showed the in vitro activity of CQ against COVID-19 [12]. CQ and Hydroxychloroquine (HCQ) are both being considered for the treatment of COVID-19 [13].

CQ is an aminoquinolone derivative first developed for the treatment of malaria within the 1940s [14]. It was a

first-line drug for the prophylaxis and treatment of malaria until the development of newer antimalarial drugs like mefloquine, artemisinin, and pyrimethamine [15, 16]. CQ is also may apply to treat extra-intestinal amebiasis, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) [17, 18]. HCQ is the other 4-aminoquinoline derivatives antimalarial drug synthesized in 1946 and is derived from CQ by adding a hydroxyl group into it [19]. This change makes HCQ more soluble and safer than CQ [20, 21]. It was used to treat rheumatic diseases such as juvenile idiopathic arthritis (JIA), SLE, RA, and Sjogren's syndrome [18].

HCQ and CQ are relatively safe, and the most common side effects include dermatological changes, pruritus, gastrointestinal symptoms and that can occur in up to 10% of the patients. The most severe side effects include cardiotoxicity, neuromyopathy of proximal muscles, and irreversible retinopathy which have low incidence [22, 23]. Pharmacokinetic and pharmacodynamic properties of HCQ are similar to that of CQ [24]. Due to low therapeutic index and pharmacological activities of its metabolites, assessment of CQ pharmacokinetic is necessary for its optimal clinical use [25].

Therefore, in the face of relevance of HCQ and CQ in COVID-19 pandemic, we discuss here the pharmacokinetic properties and toxicity considerations and mechanisms of CQ obtained from clinical use of this drug in different diseases. These should be considered when using HCQ and CQ for treating COVID-19-associated pneumonia.

Clinical uses

Antimalarial drugs such as the phosphate and sulfate salts of CQ have been used in the treatment and prevention of malaria [26]. Through CQ anti-histaminic activity in human, it can produce anti-inflammatory effects [27]. The in vitro antiviral activity of HCQ and CQ is that they could affect the growth of many different viruses such as SARS coronavirus [28], enterovirus EV-A71[29], Zika virus [30] and influenza A H5N1[31]. In a nonhuman primate model of CHIKV infection, CQ exacerbated severe fever and delayed the cellular immune response, caused an insufficient viral clearance [32]. CQ could be used for the treatment of infections caused by viruses requiring an acidic pH for infectivity [33]. CQ has been utilized in the therapy of HIV infection [34] and is additionally used in the medical care of human chronic hepatitis C [35].

Some facts have been reported on the efficacy of CQ in the treatment and prevention of pneumonia caused by COVID-19 at different levels of severity. Gao et al. [36] revealed that CQ phosphate is good in controlling the treatment by prohibiting the aggravation of pneumonia, upgrading lung imaging findings, developing a virus negative conversion, and reducing the disease course.

Mechanism

CQ has broad-spectrum activity against a range of viral, fungal, and bacterial infections [37–40]. In in vitro study, CQ has antiviral activity against RNA viruses [41]. CQ can interfere with viral particles that bind to their cellular cell surface receptor. It can inhibit quinone reductase 2 [42] that are participated within the biosynthesis of sialic acids [43]. The broad antiviral spectrum of this drug may be because of interference of CQ with sialic acid biosynthesis. Sialic acids are present on cell transmembrane proteins as important components of ligand recognition [44]. So it interferes with the fusion process of SARS virus [44]. The virus use cell surface receptor ACE2, and CQ inhibiting COVID-19 binding to target cell by interfering with glycosylation of ACE2 receptor. SARS-CoV upregulated the ACE2 expression in lung tissue thus viruses' replication and outbreak may increase [45]. By interfering with the pH-dependent endosome-mediated viral entry of enveloped viruses through alkalization of endosomes CQ can impress another stage of virus replication [46–48]. Entry into the endosome could be necessary for the viral genome to be released into the cytoplasm of infected host cells [49]. But how changes in pH could affect the integrity of viral genome is unclear [50]. It can also interfere with the post-translational modification of viral proteins [51, 52]. So that, by interfering with proteolytic processing of the M protein, it could alter virion assembly and budding [13]. Also CQ and HCQ inhibit autophagy by preventing the fusion of the autophagosome with the lysosome and deacidifying the lysosome and they have shown efficacy against many different types of viruses [53] including SARS-CoV-2 [54–56].

Through regulation of pro-inflammatory cytokines and cell signaling, CQ can affect the immune system [57]. One of the effects of CQ on the immune system is the enhancement of human cytotoxic CD8 + T and increasing the cross-presentation of viral antigens [50]. In addition, it can effect on regulation of pro-inflammatory cytokines and cell signaling by inhibiting the Toll-like receptor pathway [58]. Also CQ can inhibit virus replication through inhibition of p38 mitogen-activated protein kinase (MAPK) (Fig. 1) [59–61].

Absorption

The absorption of CQ was rapid and almost completed; so that it's oral tablets have a bioavailability of 67–114% [62]. HCQ like CQ is also fully and quickly absorbed after oral administration [63]. When administered with food, the mean plasma peak concentrations were significantly higher but the time to reach the peak concentration

Fig. 1 Possible effects of CQ on the SARS-CoV-2 replication cycle. (1) CQ interferes with glycosylation of ACE-2 receptor. Also it could limit the biosynthesis of sialic acids that may be required for cell surface binding of SARS-CoV-2. (2) CQ interferes with the pH-dependent-endosome-mediated viral entry of enveloped viruses through alkalization of endosome. So, it can inhibit fusion of the viral envelope and phospholipidic membrane of the endosomes resulting in release of the viral genome into the cell cytoplasm. (3) CQ interferes with post translational modification of viral proteins. CQ also interferes with proteolytic processing of the M protein (M protein is interacting with the other proteins of the virus, and plays an essential role during viral assembly) and alter virion assembly and budding. (4) CQ inhibits the activation (phosphorylation) of p38 MAPK. Also, it may inhibit virus replication
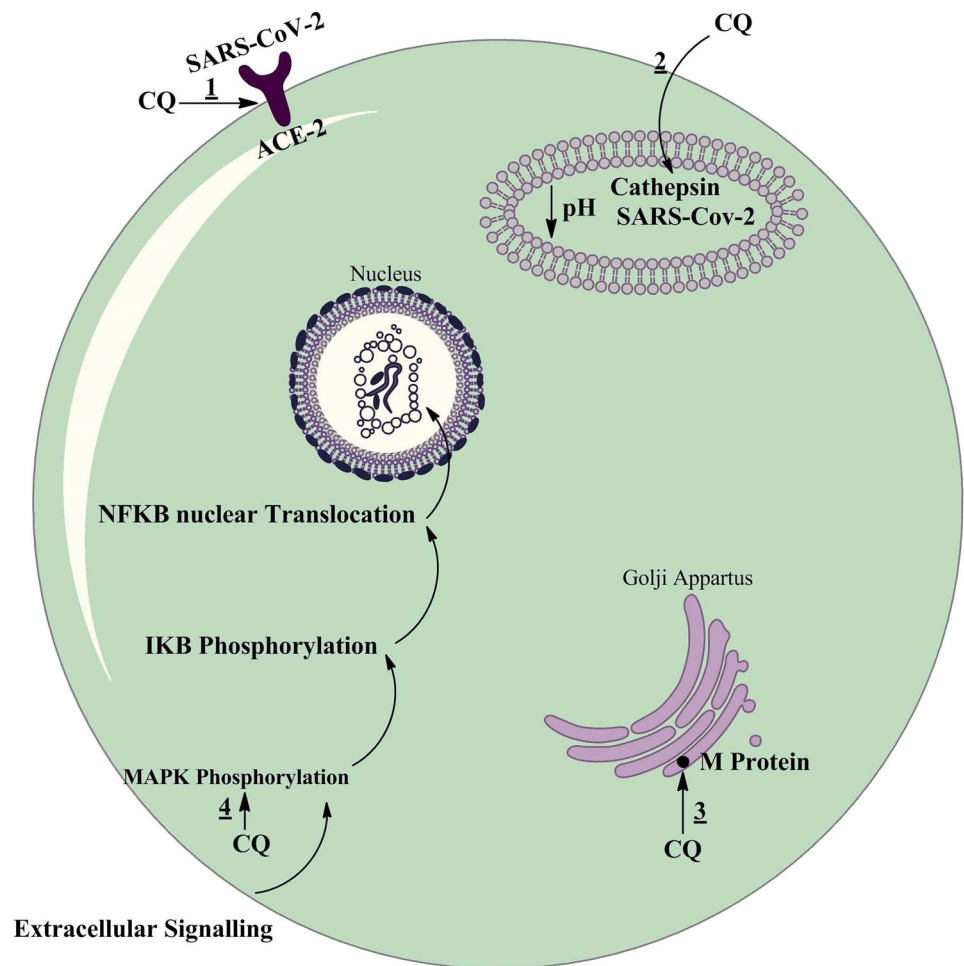
was similar. However, the effect of food seems to be subjected to large inter-individual variability. Also, the bioavailability of CQ is significantly enhanced when given along with food [64].

Distribution

Apparent volume of distribution (Vd) of CQ is 200–800 L/kg when calculated from plasma concentrations, and protein binding of CQ is about 60% [65–68]. CQ and HCQ accumulate in different tissues in varying concentrations [69]. High concentrations of these drugs are found in the cardiac tissue, lungs, kidneys, liver, skeletal muscle, skin, and eye [69]. Due to significant interindividual pharmacokinetic variability, after administration of standardized doses, variable tissue concentrations might be found [25].

Metabolism

Following single or multiple doses there are determined interindividual variations in the pharmacokinetics of CQ [67, 70–74]. About 30–50% of an administered dose of CQ is transformed by the liver [73]. After administration, CQ is rapidly dealkylated into the pharmacologically active metabolites such as bisdesethylchloroquine (BDCQ), desethylchloroquine (DCQ), and 7-chloro-4-aminoquinoline [64, 65, 70, 72] (Fig. 2). These metabolites have been involved in CQ-induced heart failure (cardiotoxicity) [74, 75]. It has been demonstrated that BDCQ is more cardiotoxic than CQ [75]. Like CQ, DCQ was showed to be active against the Zika virus [76]. Nonetheless, no data are available on the performance of DCQ in COVID-19 [77]. Studies show the minimal contribution of BDCQ formation in the metabolism of CQ in comparison with DCQ [77].
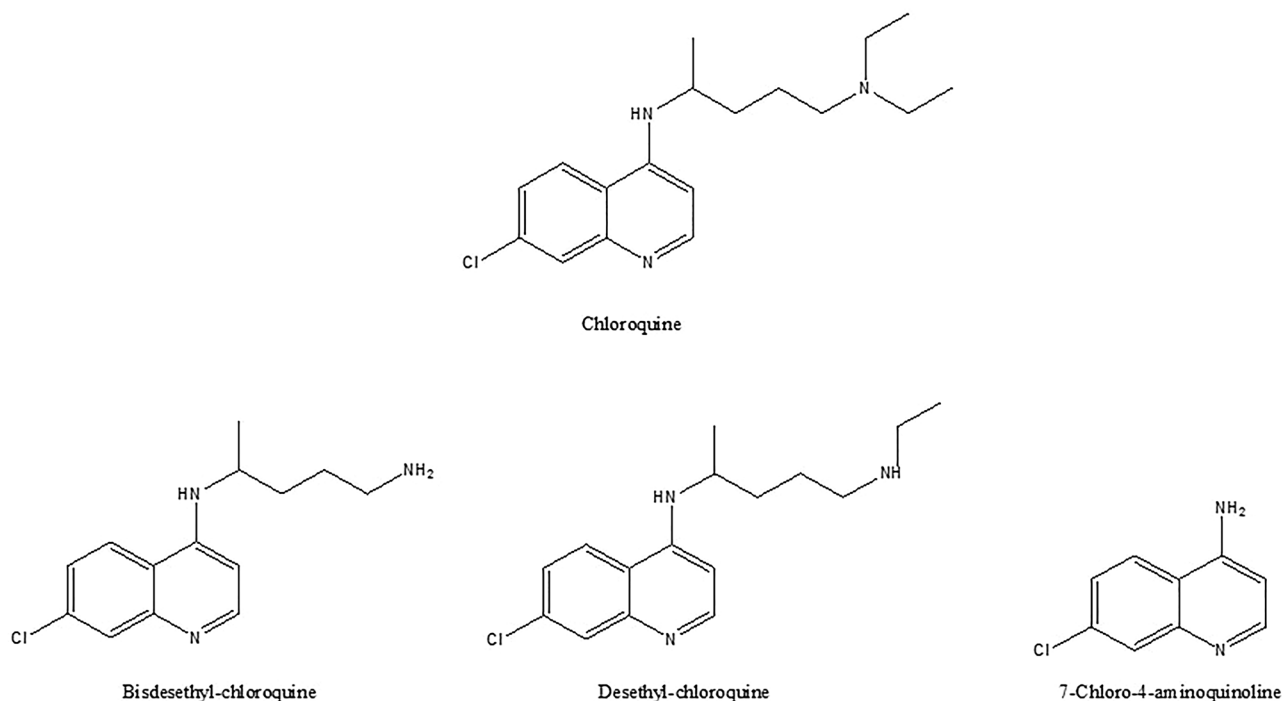
Fig. 2 Chemical structures of chloroquine and of its three main metabolites, bisdesethylchloroquine, desethylchloroquine and 7-chloro4-aminoquinoline (ChemDraw)

CQ and its active metabolites have long half-lives [74]. CQ can be *N*-dealkylated via the cytochrome P450 (CYP) enzyme system [69, 78]. Individual CYP data indicate that CYP2D6 is a main isoform of CQ metabolism, but different results showing a relatively weak relationship between the CYP2D6 and the formation of DCQ [63]. When the inhibition of the DCQ formation was estimated, by CYP-selective inhibitors, ketoconazole (a potent inhibitor of CYP3A4/5) and quercetin (a CYP2C8 inhibitor) showed a significant inhibition [61, 78]. The other CYP-selective chemical inhibitors showed weak inhibition of the metabolism of CQ [61]. So that, the CYP3A4/5 and CYP2C8 are the main enzymes in the CQ N-deethylation into DCQ [61]. Also, HCQ is a substrate of CYP2D6, CYP3A4/5, and CYP2C8 and it leads to CYP2D6 inhibition [79]. It has been indicated that CQ-induced pruritus may be related to the activity of CYP2C8 and CYP3A4/5 [61]. Nonetheless, CYP2D6 and CYP3As are 2 major isoforms involved in and affected by the metabolism of CQ [80].

Excretion

Both CQ and HCQ concentrations decrease slowly with elimination half-life of twenty to sixty days. Despite its long half-life, CQ has a relatively high total clearance, 0.7–1 L/h/kg from plasma and approximating 0.10 L/h/kg from whole blood. Its excretion is ≥ 50% as unchanged drug in urine, where acidification of urine will increase its elimination [66, 73]. Kidneys excreted 50% of CQ, therefore it is suggested that lowered doses must be consumed in patients with renal impairment. More than 50 mg/day of CQ should not be used in patients with a glomerular filtration rate (GFR) of 10–20 mL/min [81].

Toxicity

1) Nervous toxicity

CQ and HCQ are extremely toxic in overdose. Overdose of CQ and HCQ causes rapid onset of central nervous system toxicity (coma and seizures). CQ and HCQ can cause psychosis, mania, depression, paranoia, catatonia, hallucinations, suicidal ideation agitation, insomnia and confusion during acute or chronic use [82–85].

2) Cardiovascular toxicity

Overdose of CQ and HCQ causes cardiovascular collapse by inhibiting of cardiac potassium and sodium channels, which cause QRS widening and QT interval prolongation and hypokalemia resulting from intracellular shifting [86]. CQ induced cardiac toxicity indicates itself in the form of cardiomyopathy and conduction disorders [87]. Therapeutic doses cause QT interval prolongation, T wave inversion, and ST-segment

depression in resting electrocardiogram [88]. Clinical manifestations of congestive heart failure usually occur years after a third degree AV block [89]. Also, cardiovascular collapse and hypotension can occur about 2 h after overdose [89]. In patients that use CQ for LE and RA, because of increasing number of CQ cardiotoxicity cases at low doses and difficult diagnosis, an electrocardiogram (ECG) should be included with annual ophthalmological check-ups [90–92]. Furthermore, if CQ-induced cardiotoxicity detected early through ECG, it can improve the patient outcome [93].

3) Ocular toxicity

Ocular toxicity is caused by HCQ and CQ to various parts of the eye such as the retina, ciliary body, and cornea. High daily dosage and long exposure associated with toxic retinopathy, and it was the main side effect of CQ and HCQ therapy [94]. HCQ and CQ bind to the melanin of the retinal pigment epithelium (RPE), inhibited RPE lysosome activity and reduced phagocytosis of shed photoreceptor that all resulted in clinical degeneration of RPE cells [95]. Early retinal toxicity may be asymptomatic but patients with advanced stage of toxicity may complain of paracentral scotomas or color vision changes. While toxic retinopathy is usually irreversible, early detection is the best treatment [96]. The risk of retinal toxicity can be kept at low levels through paying attention to appropriate dosing and risk factors such as tamoxifen usage and renal disease [97]. Corneal deposits observed within the first 2 or 3 weeks of HCQ and CQ treatment due to binding of drug to cellular lipids and deposition of the drug in the basal epithelial layer of the cornea. Haloes and glare are symptoms of corneal deposits, and keratopathy appear most often with CQ than HCQ, and these symptoms may also vanish with dose reduction [94].

4) Enhance oxidative stress

Some studies have indicated that CQ inhibited CYP450 activity and lead to inhibition of the mitochondrial functions, and oxidative stress, particularly in erythrocytes [98, 99]. CQ could enhance oxidative stress by diminishing non-enzymatic and enzymatic antioxidant defenses, and causing DNA damage in brain, liver, and kidney of rats [100]. Studies have demonstrated that ROS (reactive oxygen species) arising, a metabolite of CQ, mediated oxidative stress and affect antioxidant enzymes in humans [101, 102].

5) Serum abnormalities

Omotosho et al. [103, 104] studied on hematology and serum biochemistry of male Wistar rats treated with CQ and showed that there is a significant decrease in a type of infection-fighting WBC called neutrophils in CQ treated group. CQ can suppress the cytokine storm in COVID-19 patients through inhibiting the production and release of IFN γ, IL-1, IL-6, and TNF α.

There was a considerable increase in serum creatinine level in the CQ treated group, which is usually seen in renal functional impairment. AST and ALT levels were significantly elevated, which shows that therapy with CQ has the potential of causing skeletal muscle, erythrocytes, hepatocytes, or necrosis of the myocardial cells that may be related to duration and dose of the therapy [104]. Also hypokalemia is present in overdose [105].

6) Other toxicities

Other toxicities of CQ include affecting on serum glucose levels and caused hypoglycemia through increasing insulin sensitivity, reducing insulin clearance, and enhancing pancreatic insulin release [106, 107], interfering with hemoglobin (Hb) clearance pathway, thereby inhibiting heme detoxification, heme–iron recycling, and causing anemia [108], neuromuscular effects such as myopathy [93], and extrapyramidal syndrome [109]. CQ and HCQ interfere with ventricular repolarization, causing QT prolongation, which could increase the risk of torsades de pointes [110]. Pruritus, headaches, dizziness, and gastrointestinal upset are common, non-ocular side effects of CQ and HCQ and discoloration of hair, skin, nails, and the oral cavity are the other rare side effects [111]. Hearing loss is typically bilateral, mild to moderate, and may be accompanied by vestibular dysfunction including vertigo [112].

Due to lower level of tissue accumulation, HCQ has fewer side effects than CQ [58]. While CQ exerts different severe side events on fetal development, HCQ is strongly suggested for pregnant patients with an autoimmune disorder because it prevents the event of development of inborn heart block because of a possible inhibitory effect of production of type I interferon (INF-I) [113, 114]. The outbreak of SARS-CoV-2 has engaged several pregnant females at high risk of infection; HCQ, instead of CQ, must be considered as a suitable therapy for these patients, given its safety profile in pregnancy condition [115, 116]. Some examples of the toxicity/side effects of CQ and HCQ in human, animal and cell lines are listed in Table 1.

Possible drug interaction

Pharmacodynamic drug–drug interactions (DDIs) occur when there is an antagonistic or synergistic effect of two or more drugs at a specific receptor site. Combinations of HCQ and CQ with other QT-prolonging medications, such as anti-emetics (e.g. ondansetron, droperidol, haloperidol, and promethazine), amiodarone, tricyclic antidepressants, quinolones, methadone, and numerous others may elevate

Table 1 The toxicity/side effects of CQ and HCQ in human, animal and cell line

Drug	Concentration/dose	Route of administration	Duration	Species/cell line	Toxicity/side effects	Mechanism of toxicity	References
CQ	25, 50, 75,100 and 500 μM	–	12, 24 and 48 h	Schwann cells	Inner glial cells toxicity	Ascorbic acid prevented CQ-induced ROS production and CQ toxicity	[113]
CQ	10–250 μM	–	24 h	ARPE-19 Cells	Retinotoxicity	Activation of autophagy and causing cell death	[114]
CQ	50 mg/kg/day	Oral	4 weeks	Rat	Kidney toxicity	Inhibiting cAMP/PKA/AKT signaling pathway	[115]
CQ	32 mg/kg	Subcutaneously	1 day	Female Mice	Pruritus side effect	Green synthesized ZnO NPs affect the CQ-induced pruritus	[116]
CQ	50 mg/kg/day	Oral	2 months	Rat	Cardio toxicity	Via up-regulation of Rho-kinase1	[117]
CQ	a) 100–300 g b) > 300 g c) Patients who never received chloroquine	Oral	3 months	Human	Macular toxicity	Depends on APO E genotype	[118]
CQ and HCQ	a) CQ: 250–500 mg/day b) HCQ: 200–400 mg/day	Oral	2 months	Human	Ocular toxicity	HCQ has a significantly lower risk of causing ocular toxicity than CQ for its more solubility	[119]

AKT protein kinase B, *APO E* apolipoprotein E, *APE-19* a human retinal pigment epithelial cell line, *cAMP* cyclic adenosine monophosphate, *CQ* chloroquine, *HCQ* hydroxychloroquine, *NPs* nanoparticles, *PKA* protein kinase A, *ROS* reactive oxygen species

the risk of developing a toxic arrhythmia such as ventricular fibrillation [117]. Combination of azithromycin and HCQ, one of the regimens which used for treatment of COVID-19, could theoretically increase the risk of torsades de pointes [118].

CQ and HCQ are both inhibitors of P-glycoprotein (P-gp) transport system, which is an efflux transporter, found in blood–brain barrier endothelial cells and gut luminal [119]. HCQ can increase digoxin levels and both of CQ and HCQ increasing cyclosporine levels, so they are attributable to HCQ and CQ inhibiting P-gp activity, insofar as both digoxin and cyclosporine are well-known substrates of this cellular pump. Additionally, there are several reports of the interaction of CQ and cyclosporine [120]. There is an increased risk for a more severe and more frequent COVID-19 clinical course for immunologically-challenged patients, so, clinicians should be especially aware of these DDIs [117].

The main family of enzymes which is responsible for oxidative metabolism of many drugs is CYP P450 system. The main metabolic enzymes of CQ and HCQ include CYP3A4/5, CYP2C8, and CYP2D6 [61, 77]. Polymorphisms in these enzymes can alter disposition [121].

Cimetidine is a CYP450 pan-inhibitor. Cimetidine leads enzymatic inhibition after several days. Then, HCQ/cimetidine and/or CQ/cimetidine co-administration results in possible increases in both HCQ and CQ levels [122]. Clinicians should also be aware that co-administration of CYP 3A4/5 inhibitors (ciprofloxacin, most macrolide antibiotics, azole anti-fungal agents, diltiazem, and verapamil, among others) and CYP2C8 inhibitors (clopidogrel and gemfibrozil) may increase the blood levels of HCQ and CQ [117]. The ability of CQ and HCQ to inhibit CYP2D6 might reduce the analgesic efficacy of opioids which are metabolised by CYP2D6 [123, 124].

Also, the co-administration of CQ with other drugs or substances that are substrates of the CYP enzymes (e.g., paracetamol and ethanol) can result in adverse effects to the kidney [125–127].

Supportive treatment and recommendation

Current advanced ocular examination methods like optical coherence tomography (OCT), multifocal electroretinography, and fundus autofluorescence have allowed earlier recognition of retinopathy, often before patients experience symptoms [128, 129]. Once definitive symptoms of retinopathy are known, the choice to prevent medication should be created in conjunction with the patient and the prescribing physician to make sure that medical risks are controlled. The patient will be advised about the danger of further visual loss counting on the severity of the retinopathy [130]. Patients with age-related maculopathy or macular dystrophies generally are suggested to continue intake of zeaxanthin and lutein and keep away from sun exposure [94, 95]. The most necessary changes in practice guidelines include dose calculation supported total weight, dose reduction after long-term use, and intense screening with techniques including OCT after 5 years [23].

Use of general treatments including gastric lavage, fluid resuscitation, sodium bicarbonate, or single-or multiple-dose activated charcoal, were important elements in the treatment of CQ overdose. Administrations of diazepam and epinephrine and mechanical ventilation have been proposed as important factors in CQ poisoning situations [131, 132]. In addition, intravenous thiopentone administration could be effective in the treatment of cardiac arrest of patients poisoned with CQ [133]. Also, administration of hypertonic saline or sodium bicarbonate could be beneficial for substantial QRS widening and arrhythmia [134]. Studies suggest that free radical scavenging and antioxidant activity of lipoate may prevent the CQ-induced lipid peroxidation. So, lipoic acid can protect renal tissue from CQ-induced oxidative damage [135].

Stopping the drug, using supplemental glucose or parenteral dextrose, and administration of octreotide (50–100 μg subcutaneously Queryor intravenously every 8 h) are supportive treatments for management of hypoglycemia [136].

Resolution of neuropsychiatric effects is predicated upon stopping the drug, although symptoms might not resolve immediately [137].

Conclusion

For decades, CQ has been applied for the treatment of various diseases and disorders. CQ and HCQ are antimalarial, antiamoebic, immunomodulatory, and potential broad-spectrum antiviral drugs. Studies have suggested CQ and HCQ can interfere with ACE2 receptors glycosylation of the coronavirus, increase endosomal pH, interfere with post translational modification of viral proteins, inhibit the activation of p38 MAPK thus inhibiting viral fusion, decreasing viral load, altering virion assembly and inhibiting virus replication.

Being aware of ADMET considerations for CQ and also biochemical and hematological changes through taking CQ in patients could help us to reach optimal efficacy and lower toxicity. Through the study of pharmacokinetics of CQ, we observed that CQ and HCQ have rapid gastrointestinal absorption [62], a high volume of distribution, long half-lives [66, 73] and pharmacologically active metabolites [73].

COVID-19 has rapidly increased in epidemic scale since its first appearance in Wuhan, China, in December 2019[138]. There are limited data to support the use of CQ and HCQ for COVID-19. The drugs have some in vitro activity against several viruses, including influenza and coronaviruses, but previous randomized trials in patients with influenza have been negative [139, 140]. One small nonrandomized study from France showed benefit of CQ and HCQ, and a follow-up study still lacked a control group [141, 142]. Another randomized and small study in patients with mild to moderate COVID-19 from China showed no difference in recovery rates [143]. Other clinical trials from China have already shown promising results for using these drugs in COVID-19 [144, 145]. In a small sample size study, HCQ therapy was significantly associated with a reduction in viral load and worked synergistically with azithromycin against COVID-19. In an in vitro study, a similar synergistic effect was obtained in combination therapy of HCQ and azithromycin, as both reduce the acidity of the lysosome to impair viral replication. On the other hand, a high risk of HCQ's QT prolongation was observed with concurrent treatment with azithromycin [141, 146, 147]. Reports of adverse events have increased and several countries reporting poisonings. Common side effects of CQ and HCQ are retinopathy, mental status changes, and hypoglycemia. In patients receiving these drugs, clinical screening for visual and mental disturbances, glucose levels, hepatic and renal function, and monitoring of heart rate and the QT interval are recommended. Recent studies have shown that CQ can decrease in neutrophil count [104] and it could be beneficial in COVID-19 related neutrophilia. COVID-19 can increase secretion of hyperglycemic hormones, and cause hyperglycemia but CQ may decrease serum glucose levels as an adverse effect, so CQ can control COVID-19 induced hyperglycemia. However, there was a significant increase in ALT and AST levels in the CQ treated group, like COVID-19 patients, so the potential of causing necrosis of the hepatocytes, skeletal muscle, erythrocytes, myocardial cells or in CQ treated COVID-19 patients may increase. Also, elevated serum creatinine in CQ treated group especially in COVID-19 patients could increase renal functional impairment. With the multiple DDIs that are currently known, use of CQ and HCQ with other drug therapy requires consideration for patient safety.

While further clinical trials are required to provide concrete evidence on the use of these agents in COVID-19.

Declarations

Conflict of interest Authors have no conflicts of interest.

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