



Review article

Chloroquine to fight COVID-19: A consideration of mechanisms and adverse effects?

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ABSTRACT

The COVID-19 outbreak emerged in December 2019 and has rapidly become a global pandemic. A great deal of effort has been made to find effective drugs against this disease. Chloroquine (CQ) and hydroxychloroquine (HCQ) were widely adopted in treating COVID-19, but the results were contradictory. CQ/HCQ have been used to prevent and treat malaria and are efficacious anti-inflammatory agents in rheumatoid arthritis and systemic lupus erythematosus. These drugs have potential broad-spectrum antiviral properties, but the underlying mechanisms are speculative. In this review, we re-evaluated the treatment outcomes and current hypothesis for the working mechanisms of CQ/HCQ as COVID-19 therapy with a special focus on disruption of Ca²⁺ signaling. In so doing, we attempt to show how the different hypotheses for CQ/HCQ action on coronavirus may interact and reinforce each other. The potential toxicity is also noted due to its action on Ca²⁺ and hyperpolarization-activated cyclic nucleotide-gated channels in cardiac myocytes and neuronal cells. We propose that intracellular calcium homeostasis is an alternative mechanism for CQ/HCQ pharmacology, which should be considered when evaluating the risks and benefits of therapy in these patients and other perspective applications.

1. Introduction

The outbreak of COVID-19 at the end of 2019 has caused more than ten million confirmed infections and over half a million deaths. Despite strong mobilization and disease containment, the pandemic has spread worldwide. There have been many attempts to cure and mitigate the effects of SARS-CoV-2 infection, but an effective treatment is still highly desired. Among the treatments used so far, two structurally related quinoline drugs, chloroquine (CQ) and hydroxychloroquine (HCQ), have been widely adopted for prophylaxis, compassionate use or clinical trials (Arshad et al., 2020; Boulware et al., 2020; Chen et al., 2020b; Gao et al., 2020; Gautret et al., 2020; Huang et al., 2020; Molina et al., 2020; Principi and Esposito, 2020; Rosenberg et al., 2020; Yu et al., 2020), however, these studies have yielded conflicting reports. This prompted us to reconsider the proposed mechanisms of action of CQ/HCQ (MOA).

2. Clinical use and mechanisms

2.1. Current hypothesis

As a generic drug, quinine was initially employed to treat malaria but has since been succeeded by chloroquine and its derivative, hydroxychloroquine. These drugs were later used for rheumatoid arthritis and systemic lupus erythematosus (Rainsford et al., 2015). Their mechanisms of action and side effects are similar, and have been well reported (Frisk-Holmberg et al., 1983; Korinichona et al., 1992; Maxwell et al., 2015). More recently, CQ/HCQ was evolving to be deployed to treat several viral infections, such as Borna disease, hepatitis A and AIDS (Savarino et al., 2003). Encouraged by successful clinical use for these infectious diseases, Savarino and colleagues first proposed that CQ/HCQ may be repurposed to treat coronavirus during the severe acute respiratory syndrome (SARS) outbreak in 2003 (Savarino et al., 2003). This hypothesis was soon validated by *in vitro* studies which demonstrated

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inhibition of SARS-CoV (Keyaerts et al., 2004; Vincent et al., 2005). Clinical studies were not proceeded as SARS pandemic was put out quickly, but using animal models, CQ has been revealed to have antiviral activity against human coronavirus OC43 (Keyaerts et al., 2009). Wang and colleagues were amongst the first to perform *In vitro* studies demonstrating inhibition of SARS-CoV-2 (Wang et al., 2020), prompting widespread clinical interest in CQ/HCQ, but the efficacy and underlying MOA remains debatable (Cortegiani et al., 2020; Touret and de Lamberie, 2020).

A long standing hypothesis suggests that CQ/HCQ may exhibit effects on coronavirus through two different mechanisms: pH elevation of endosomes/lysosomes and immunity modulation (Figure 1A,B) (Savarino et al., 2003; Tripathy et al., 2020; Zumla et al., 2016). The pH regulation may be a common mechanism for malaria and COVID-19. For antimalarial use, CQ/HCQ can be trapped in food vacuoles of the parasite, a lysosome-like organelle, where it inhibits formation of hemozoin (from the heme released by digestion of hemoglobin) and accumulates waste, leading to parasite death (Sullivan et al., 1996). Likewise, CQ/HCQ in its unprotonated form can diffuse passively across cellular membranes where it becomes protonated and trapped in the endosomes/lysosomes, alkalinizing these acidic compartments. This alkaline environment may block viral entry into vulnerable host cells (Figure 1A) as SARS-CoV-2 entry is facilitated by spike protein with the host cell factors (ACE2), and this process employs serine protease TMPRSS2 for spike protein priming, whereas the TMPRSS2 priming uses endosomal cysteine proteases cathepsin B/L that requires low pH (Hoffmann et al., 2020a). Furthermore, when endosomes fuse with lysosomes, the high pH can also prevent viral envelope from breaking and liberating RNAs into host cells. Additionally, it also inhibits viral RNA replication as relevant enzymic functions are compromised by an elevated pH. This hypothesis was supported by well-designed *in vitro* study: when the Vero E6 culture was inoculated with SARS-CoV in presence of CQ, potent anti-viral activity can be observed; whereas when CQ was added later, anti-viral activity diminished (Keyaerts et al., 2004). However, this result could not be duplicated in Calu-3 lung cells (Hoffmann et al., 2020b) and human airway epithelium (Maisonasse et al., 2020). It should be noted that pH elevation by ammonium chloride can block infection of 293T and Caco-2 cell lines (Hoffmann et al., 2020a), and the failure in lung cells is likely attributed to cell types. The experiment on primary epithelial cells

has not yet to be done, and more work is needed to validate this hypothesis. The cell line independent effects implicate that CQ/HCQ may be beneficial via some types of cells (such as kidney cells) rather than lung cells, as COVID-19 is not a typical pneumonia and it can be more broadly defined as system disease for multiple organs being infected. Besides, several other postulations were proposed as well. It should be noted that through regulating endosome/lysosome function on vasculature, CQ/HCQ may serve as an anti-thrombotic agent to improve hypoxia commonly found in acute respiratory distress syndrome (ARDS) (Ackermann et al., 2020; Jung et al., 2010; Maes et al., 2016). Though the evidence is limited, this is of interest as blood clotting is one of the major fatal processes in COVID-19.

The immunity hypothesis was derived from the successful use of CQ/HCQ in rheumatoid arthritis and lupus erythematosus to suppress inflammation by decreasing proinflammatory cytokine production (Fox, 1993; Rainsford et al., 2015). In this scenario, CQ/HCQ may play a role in COVID-19 as an immunomodulant to suppress fatal hyperinflammation (Mehta et al., 2020). However, despite suppression of the cytokine storm is beneficial in severe COVID-19 cases, this may also disrupt the ability to process antigen and the subsequent immune response, which may have adverse consequences in combatting viral infection. In addition, chloroquine might affect antigen-antibody interaction, thereby compromising immune neutralization to coronal virus when used for prolong time or under high dosages (Edwards et al., 1982). Therefore, the ultimate effects of CQ/HCQ on the innate immune response to SARS-CoV-2 remains to be determined (Meyerowitz et al., 2020).

2.2. Calcium homeostasis as an emerging antiviral target?

As virus exploits the machinery and intracellular environment of a host cell for viral lifecycles, there are several other likely targets critical for RNA duplication, transcription or budding (Clark and Eisenstein, 2013; Schoeman and Fielding, 2019). One potential target is calcium channels and intracellular calcium pool. CQ/HCQ appears to serve as an antagonistic agent to modulate slow calcium channels in atrial trabeculae (Filippov et al., 1989), calcium signaling in primary B lymphocytes (Wu et al., 2017) and murine CD4⁺ Thymocytes (Xu et al., 2015). Xu and colleagues further proved that chloroquine inhibits IP₃R-mediated Ca²⁺ release from intracellular stores and TRPC3 channel mediated Ca²⁺

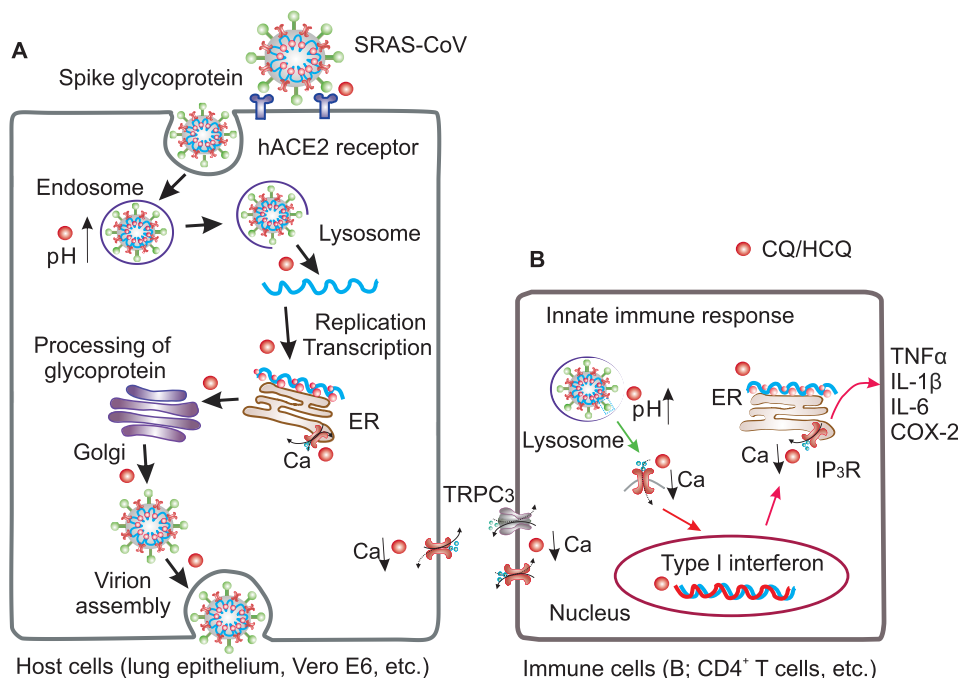


Figure 1. Highlights of SARS-CoV-2 lifecycle and proposed mechanisms of CQ/HCQ interruption of virulence: 1) modulation of endosome or lysosome function by elevation of pH, thereby interrupting virus entry, as acidic pH is required for glycosyltransferases to modify envelope glycoprotein. CQ/HCQ impairs viral spike proteins binding with ACE2 receptors, thereby blocking virus-host cell fusion; Note that solid black arrows indicate the critical phases by which CQ/HCQ may disrupt the lifecycle of coronavirus (A). 2) Modulation of cytokine production (TNF α , etc.) and antigen presentation. The typical innate response to SARS-CoV-2 is marked by type I interferon. The anti-inflammatory property is proved effective for rheumatoid arthritis and lupus (B); 3) Intervention of intracellular calcium gradients, impairing RNA replication, spike glycoprotein production, and innate inflammatory response. Alternatively, attenuation of Ca²⁺ influx through viroporin (Green arrow) to mediate proinflammation (B). ER. Endoplasmic reticulum; hACE2, human angiotensin-converting enzyme 2; TNF α , tumor necrosis factor α .

influx in CD4⁺ T cells (Figure 1B). Interestingly, our previous work demonstrated that quinine can reversibly block hyperpolarization-activated cyclic nucleotide-gated (HCN) channels in dopaminergic neurons (Zou et al., 2018), which is weakly permeable to Ca²⁺, implicating an alternative mode of action by quinolone drugs (Postea and Biel, 2011). Furthermore, our preliminary data showed that compartmental Ca²⁺ concentration in cortical neurons derived from human induced pluripotent stem cells (iPSCs) is differently attenuated by chloroquine. This data suggests that chloroquine can modulate intracellular Ca²⁺ by attenuation both extracellular Ca²⁺ entry and intracellular store-operated calcium (SOC) release. Therefore, CQ/HCQ may alternatively block virulence by interfering cytosolic Ca²⁺ required for viral lifecycles in vulnerable cells, such as airway epithelial cells, pulmonary capillary endothelial cells and other types of cells (Wiersinga et al., 2020; Zhang et al., 2020) (Figure 1A).

Targeting host store-operated Ca²⁺ release has been suggested a general strategy to attenuate viral infection (Clark and Eisenstein, 2013; Zhou et al., 2009). In fact, Ca²⁺ involvement in viral replication, budding or shell assembly has been demonstrated in a number of viruses, such as rotavirus, Dengue virus, polyomavirus, bovine herpesvirus and Hepatitis A or B virus (Bishop and Anderson, 1997; Cui et al., 2019; Dionicio et al., 2018; Geng et al., 2012; Han et al., 2015; Li et al., 2003; Lobeck et al., 2016; Sun et al., 2017; Zhang et al., 2016; Zhu et al., 2017), it is highly plausible for RNA replication in coronaviruses as well. In addition, spike protein of SARS-CoV was revealed to induce an influx of extracellular Ca²⁺, leading to activation of a Ca²⁺-dependent protein kinase C alpha (Liu et al., 2007). This process is critical for SARS-associated coronavirus activated cyclooxygenase-2 (COX-2) expression, as the PKC alpha modulates downstream ERK/NF-kappa B pathway, which is required to activate COX-2 protein, a putative marker of inflammatory response. Thus, CQ/HCQ may modulate inflammatory responses by blocking Ca²⁺ influx into host cells. Further, CQ/HCQ may directly modulate virulence by affecting coronavirus envelope (E) protein Ca²⁺ transport. SARS-CoV E protein is a viroporin which allows Ca²⁺ and other cations to pass through. This is a critical process to trigger proinflammation, such as IL-1 β , a potent cytokine (Figure 1B). SARS E protein can even form a protein-lipid channel in Golgi membrane by which Ca²⁺ can mediate pH and E protein pore selectivity. Therefore, CQ/HCQ may alternatively modulate immune reaction by blocking Ca²⁺ influx through viroporin and suppression of SARS-CoV-2 derived, exacerbated pro-inflammation (Nieto-Torres et al., 2015; Schoeman and Fielding, 2019). Furthermore, CQ/HCQ may serve as an immunomodulator by blocking Ca²⁺-dependent calcineurin activity (Tanaka et al., 2013), as the inhibition of calcineurin blocks the translocation of nuclear factor of activated T cells, thereby prevent the transcription of cytokine. These lines of evidence suggests that cytosolic Ca²⁺ modulation may be an underlying mechanism through which CQ/HCQ serves as a broad-spectrum antiviral agent (Clark and Eisenstein, 2013; Keyaerts et al., 2004, 2009; Vincent et al., 2005; Yan et al., 2013). Given the above-mentioned considerations and the close phylogenetic relationship between SARS-CoV and SARS-CoV-2, targeting on calcium is likely to be a part of CQ/HCQ effects for COVID-19.

2.3. The CQ/HCQ efficacy in line with the pathogenesis of COVID-19

The discrepancy between the results of *in vitro* studies showing efficacy of CQ/HCQ and the results of clinical trials has been frustrating. While several reports have implied an improved efficacy administered alone or with a concomitant use of azithromycin or zinc (Gautret et al., 2020; Yu et al., 2020), limited benefits for either prophylaxis or treatment have also been reported (Boulware et al., 2020; Magagnoli et al., 2020; Wiersinga et al., 2020). Presumably, Ca²⁺ dynamics is different *in vitro* and *in vivo* and Ca²⁺ homeostasis in COVID19 patients is likely to

change during the disease progress from the prodromal, to the mild and severe phases. In these different phases, symptoms of COVID-19 become highly heterogeneous. This involves respiratory and kidney failure, leading to hypoxia and dysfunctional homeostasis. On the other hand, *in vitro* study is well controlled for variables such as temperature, pH, oxygen and ion gradients, which may not be achieved when there is impaired pulmonary, renal and circulatory function (Takahashi and Suzuki, 2015). Of note, Low plasma pH is associated with low CQ/HCQ concentration in endosome/lysosome and high probability of blood coagulate (Crowell and Houston, 1961; Warhurst et al., 2007). With these consideration, Zn²⁺ and Azithromycin have been commonly used as adjuvants in combination with CQ/HCQ to achieve synergistic effect (Retallack et al., 2016; Schogler et al., 2015; te Velthuis et al., 2010; Xue et al., 2014; Zhu et al., 2013), as both agents have anti-viral properties. Specifically, CQ/HCQ is also suggested to be an Zn²⁺ ionophore to increase Zn²⁺ influx, contributing versatile actions within endosome/lysosome (Skalny et al., 2020; te Velthuis et al., 2010; Xue et al., 2014). We suggest that plasma Zn²⁺ test along with CQ/HCQ concentration assay is much needed in future clinical application. In contrast to the CQ/Zn²⁺ synergistic effect, there is no pharmacokinetic interaction between azithromycin and chloroquine (Cook et al., 2006). However, like CQ/HCQ, azithromycin can also act as anti-viral agent through impairing lysosome function or several other possible means (Damle et al., 2020; Nujic et al., 2012).

3. Adverse effects and mechanisms

3.1. Major adverse effects

It is well established that quinoline drugs affect excitable cells, including cardiac myocytes and neurons, through modulation of cellular excitability and action potential (Wenzel and Kleoppel, 1980; White, 2007; Zou et al., 2018). Indeed, CQ/HCQ has broad effects on HCN channels and inwardly rectifying K⁺ channel 2.1 (Kir2.1), as both channels are phylogenetically related (Rodriguez-Menchaca et al., 2008). In addition, the HCN regulates rhythmic activity in both spontaneously spiking neurons (HCN1, 2, 4) or pace making sinoatrial myocytes (HCN3). Consequently, CQ/HCQ can mediate rhythmic activity of sinoatrial cardiac myocytes and affects heart contractility (Capel et al., 2015; Rodriguez-Menchaca et al., 2008) (Figure 2).

The effects of CQ/HCQ on HCN is our major concern as it causes a delayed action potential in neurons and QT interval prolongation in cardiac myocytes (Figure 2) (Haeusler et al., 2018; Postea and Biel, 2011; Zou et al., 2018). The CQ/quinine adverse effects found in *in vitro* studies is quite similar with the clinical outcomes: both quinine and chloroquine appeared to cause a decrease of myocardial cell discharge and lead to aberrant cardiac electrical conduction and QT elongation (Figure 2). CQ also targets on nicotine receptors in neurons, thus it might affect intracardiac nerve-cardiac signaling mediated by nicotine receptors, thereby contribute to mediate the excitability of cardiac myocytes (Ballesterio et al., 2005; Duraes Campos et al., 2018; Estes et al., 1987). In a small clinical trial, the mean QT prolongation was about 35 (28–43) ms and more than 20% percent of COVID-19 patients had a QT interval exceeding 500 ms during chloroquine treatment (van den Broek et al., 2020), but in general CQ/HCQ is safe even QT prolongation is commonly reported (Sarayani et al., 2020). In rare cases, this may lead to ventricular arrhythmias, insufficient ventricular blood reflux or ejection, and sudden death. Thus, it should be careful when treating COVID-19, as in severe cases of this disease, there is increased cardiac burden due to ARDS, and possibly direct cardiac injury (Chen et al., 2020a; Yang et al., 2020). As for those with comorbidities such as heart diseases, including tachycardia, bradycardia, cardiomegaly and arrhythmia (commonly found in older patients) (Xiong et al., 2020), special caution should be taken

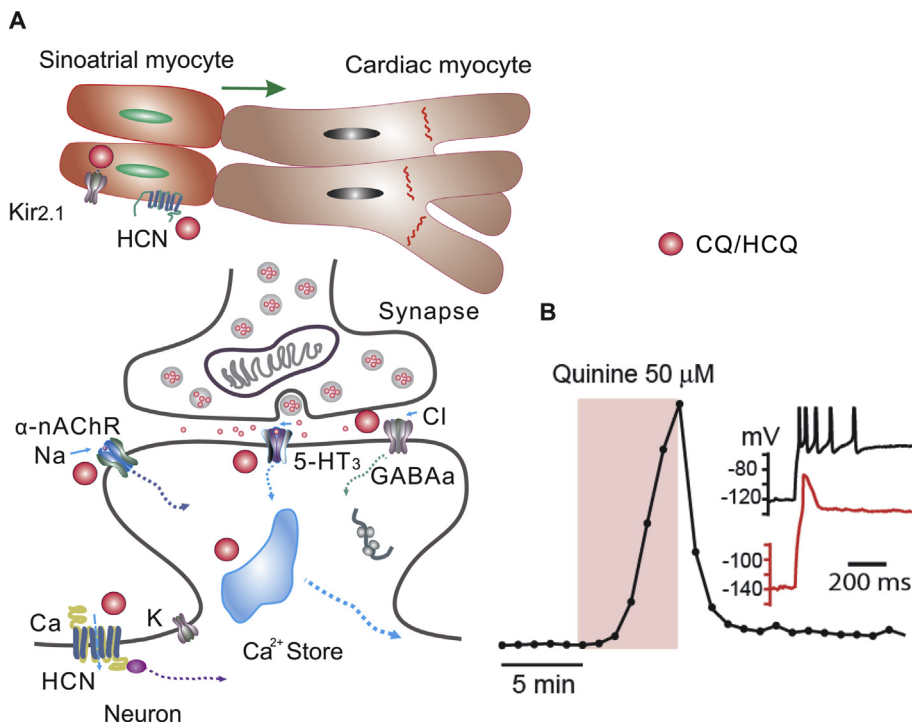


Figure 2. Quinolines have major adverse effects through neurons and cardiac myocytes. A. HCN and potassium channels are expressed in both types of cells. Chloroquine diffuses into cells and binds the cytoplasmic pore domain of Kir_{2.1} (A). The effect on HCN and K channels on sinoatrial myocytes lead to slower pace-making activity, whereas the effect on cardiac myocytes leads to decreased excitability and aberrant electrical transduction from sinoatrial to cardiac myocytes (top panel in A; green arrow denotes the electric signal propagation direction from sinoatrial to cardiac myocytes), thereby causing QT prolongation and ventricular arrhythmias. CQ/HCQ also modulates neuronal function by intervention of intracellular calcium homeostasis and synaptic signaling by binding to $\alpha 9\alpha 10$ -nAChR, 5-HT₃ or GABA_A receptors, inducing fast-onset neuropsychiatric effects (lower panel in A). B. The action potential is delayed by application of quinine in a human iPSC derived dopaminergic neuron (modified from Zou et al., 2018). The drug effect is fast and partially reversible. Inset, recording traces before (black) and after (red) quinine treatment (50 μ M). GABA, γ -aminobutyric acid; 5-HT, 5-hydroxytryptamine.

(medication may discontinue) as poor cardiac function may be significantly exacerbated by CQ/HCQ toxicity. Despite the potentially fatal effect on the QT interval, CQ/HCQ has been shown to have cardiovascular benefits by inhibiting cyclooxygenase-dependent contraction (McCarthy et al., 2016). CQ/HCQ also exerts beneficial effects in experimental pulmonary arterial hypertension (Long et al., 2013).

The sensitivity of quinolines on ion channels also raises concerns for patients with metabolic abnormalities such as hypokalemia, hypomagnesemia and hypocalcemia. Discussion of other issues of CQ/HCQ toxicity, such as those related to G-6-PD deficiency, hypoglycemia and interaction with other drugs are beyond the scope of this article (Choudhry et al., 1978; Jiang, 2020; Rajeshkumar et al., 2020; Rainsford et al., 2015).

3.2. The clinical use in consideration of CQ/HCQ toxicity

The adverse effect on different types of cells renders it a tricky drug to employ for clinical applications. A review for publications concerning CQ/HCQ toxicity prior to July 2017 has revealed that disrupted electrical conduction is the underlying mechanism for 85% of cases involved in CQ/HCQ heart toxicity (Chatre et al., 2018). These papers primarily address malaria, rheumatoid arthritis and lupus erythematosus, but their clinical effects with COVID-19 are vastly different, as the latter can be complicated by ARDS and myocarditis in the late phase, with resultant tissue hypoxia and cardiac stress (Xiong et al., 2020). As the CQ₅₀ for anti-viral action is much higher than that for toxic effect on cardiac or neuronal cells (Liu et al., 2020; Rodriguez-Menchaca et al., 2008), the

effect on excitable cells, whether neurons or cardiac cells, is more rapid than its effect on viral replication and inflammation. These side effects typically appear earlier (within hours) than anti-viral effects (days), however QT prolongation may be delayed for as long as three days due to plasma binding and reduced bioavailability (Chorin et al., 2020). The unique pharmacokinetics of these medications facilitates easy monitoring of the toxic effect on neuronal and cardiac cells.

There are two categories of drugs often associated with QT prolongation that need to be used with caution in patients treated with CQ/HCQ - psychotropic and antiarrhythmic drugs (see Table 1) (Jiang, 2020; Maxwell et al., 2015). More drugs involved in drug-drug interaction with chloroquine and QT prolongation can be found elsewhere (CredibleMeds, 2020). Interestingly, although azithromycin can cause QT prolongation, it has been safely used in combination with hydroxychloroquine with judicious monitoring, and there was no additional QT increase (Fossa et al., 2007; Gautret et al., 2020; Sagara et al., 2014).

The possible invasion of SARS-CoV-2 into the central nervous system has been highlighted by the presence of neurological symptoms such as nausea, anosmia and seizures (Le Guennec et al., 2020; Li et al., 2020; Mao et al., 2020). Of note, cholinergic system is implicated in anti-inflammatory modulation in COVID-19 (Farsalinos et al., 2020). Given all these likelihoods, the neurotoxic effects of CQ/HCQ on the nervous system should also be considered. The non-selective action on HCN and K⁺ channels renders quinolines capable of affecting the function of multiple types of neurons and synaptic transmission, including dopaminergic, GABAergic and $\alpha 9\alpha 10$ -nAChR signaling (Figure 2A) (Ballesterio et al., 2005; Thompson and Lummis, 2008; Zou et al., 2018).

Table 1. Representative drugs with QT interval prolongation.

Drug Class	Drugs
Antiarrhythmic drugs	Amiodarone, Cordarone, Dronedarone, Ibutilide, Procainamide, Sotalol;
Antimicrobial drugs	Astemizole, Azithromycin, Clarithromycin, Erythromycin, Fluconazole, Levofloxacin, Moxifloxacin, Quinolone, Terfenadine, Voriconazole
Somatostatin Analog	Octreotide
Psychotropic	Amitriptyline, Chlorpromazine, Citalopram, Clomipramine, Droperidol, Methadone, Haloperidol
Gastrointestinal	Dolasetron, Domperidone, Ondansetron

Rarely, this may lead to epileptic seizure that should prompt discontinuation of CQ/HCQ treatment (Krzeminski et al., 2018). There are also minor adverse effects including retinopathy, ototoxicity, itching and mood disturbance, and close monitoring of the effect of CQ/HCQ on neurological or neuropsychiatric, visual and auditory symptoms will also be warranted.

4. Management

CQ/HCQ can be binding with plasma and intracellular proteins, *in vitro* testing of quinoline pharmacology typically has a delayed washout effect, while it has a long elimination half-life (22–45 days) in administered *in vivo* (Cortegiani et al., 2020; McLachlan et al., 1993; Rainsford et al., 2015; Zou et al., 2018). Animal research has demonstrated a huge disparity of HQ/HCQ concentrations in different tissues or organs with the greatest accumulation in lungs (Meyerowitz et al., 2020). In this sense, the dosage for COVID-19 is still open to explore and is a challenge to current ongoing randomized placebo-controlled clinical trials and statistic interpretation. The drug bioavailability onsite changes from patients to patients due to binding capability, body weight, gender and sickness, etc., thus a more precise group concerning binding is needed, which has so far not been reported (Arshad et al., 2020; Gautret et al., 2020; Yu et al., 2020). One report revealed that twice daily of hydroxychloroquine at 200 mg, a relatively lower dosage for 7–10 days had achieved significant efficacy (Yu et al., 2020). However, there might be better benefit and less toxic side effects by following a lower dosing regimen (four or six-times daily) with close monitoring of plasma binding. More recently, a multi-hospital study of 2541 patients revealed promising results with reducing mortality by 66% with HCQ alone and 71% with HCQ/Azithromycin, respectively (Arshad et al., 2020). It is prominent that in the settings of this study, HCQ use was administered at a low dosage regimen (400 mg for first two days, following with 200 mg) in the earlier stage of COVID-19 (within 24 h confirmed by lab) and QT was closed monitored with no documented case of torsade de pointes. Interestingly, this dosage was equivalent to that recommended for rheumatoid arthritis and lupus.

5. Conclusion

The foregoing makes clear the complexity of CQ/HCQ action on SARS-CoV-2, we suggest CQ/HCQ has limited benefits for prodromal or mild COVID-19 subjects by following a definite protocol. Among other considerations, in these patients, cardiomyocytes may be healthy and resilient enough to recover from a brief toxic shock by HCQ/CQ. However, unexpected efficacy is possible due to complicated modes of action, adverse effects or patient specific conditions (CQ/HCQ bioavailability, Ca^{2+} concentration in the extracellular media and membrane permeability caused by pH fluctuation, oxygen saturation and fever). This is highly challenging to frontline doctors, a case-by-case strategy may be the most optional way to evaluate CQ/HCQ benefits for COVID-19 and adverse effects. A closer look at the effect of CQ/HCQ on Ca^{2+} homeostasis is warranted as we aim to eliminate coronavirus infection. It remains to be further validated whether cytosolic Ca^{2+} is a target for CQ/HCQ to suppress SARS-CoV-2 and other viral infections.

Declarations

Author contribution statement

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Competing interest statement

The authors declare no conflict of interest.

Additional information

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