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To cite this article: Boscolli Barbosa Pereira (2020) Challenges and cares to promote rational use of chloroquine and hydroxychloroquine in the management of coronavirus disease 2019 (COVID-19) pandemic: a timely review, *Journal of Toxicology and Environmental Health, Part B*, 23:4, 177-181, DOI: [10.1080/10937404.2020.1752340](https://doi.org/10.1080/10937404.2020.1752340)

To link to this article: <https://doi.org/10.1080/10937404.2020.1752340>



Published online: 12 Apr 2020.



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Challenges and cares to promote rational use of chloroquine and hydroxychloroquine in the management of coronavirus disease 2019 (COVID-19) pandemic: a timely review

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ABSTRACT

As a result of the 2019 coronavirus disease pandemic (COVID-19), there has been an urgent worldwide demand for treatments. Due to factors such as history of prescription for other infectious diseases, availability, and relatively low cost, the use of chloroquine (CQ) and hydroxychloroquine (HCQ) has been tested *in vivo* and *in vitro* for the ability to inhibit the causative virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, even though investigators noted the therapeutic potential of these drugs, it is important to consider the toxicological risks and necessary care for rational use of CQ and HCQ. This study provides information on the main toxicological and epidemiological aspects to be considered for prophylaxis or treatment of COVID-19 using CQ but mainly HCQ, which is a less toxic derivative than CQ, and was shown to produce better results in inhibiting proliferation of SARS-CoV-2 based upon preliminary tests.

KEYWORDS

Toxicology; screening; health care; retinopathy; public health

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has produced significant impacts on public health and global economy, due to hospitalizations, deaths, high complexity of clinical care and long quarantine periods required to control the spread of the causative virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

In a scenario of high infection rate and occurrence of severe cases that may result in death, the demand for effective drugs to treat and control the COVID-19 pandemic was given top priority by the health and political authorities. Among the drugs currently tested *in vitro* and *in vivo*, remdesivir, ribavirin, chloroquine (CQ) and hydroxychloroquine (HCQ) have shown promising clinical results in inhibiting the viral replication of SARS-CoV-2 (Zhang et al. 2020). However, while the molecular mechanisms underlying therapeutic actions and clinical benefits remain to still be explored, the search for information regarding CQ and HCQ toxicity is a priority, since it can directly contribute to the design of randomized clinical trials (Cabral et al. 2019; Jorge et al.

2018; Liu et al. 2020; Stokkermans and Trichonas 2019; Yam and Kwok 2006; Zhang et al. 2015).

Although research concerning the use of CQ and HCQ in control of COVID-19 is still preliminary, the potential use of these drugs is supported by factors including availability, low cost, and history of use in treatment of rheumatic and infectious diseases such as malaria and amebiasis (Stokkermans and Trichonas 2019). In addition, there is a growing trend of preference for HCQ, which is a less toxic derivative of CQ, and was found to yield better results in inhibiting proliferation of SARS-CoV-2 (Liu et al. 2020).

With respect to adverse effects, there is a recognition that HCQ produces toxicity to retina tissue, which may consequently result in irreversible retinopathy (Marmor et al. 2002), especially in cases of prolonged exposure to the drug (Wolf and Marmor 2010). In less recurrent cases, usually after prolonged exposure to HCQ, cardiotoxicity, and toxicological effects were reported in the central nervous system with neuromyopathy symptoms (skeletal muscle weakness) and gastrointestinal changes (Stein, Bell, and Ang 2000).

Although there is evidence of damage to the genetic material of liver cells *in vitro* produced by antimalarial drugs (Guo et al 2019), there are few apparent studies available that address the genotoxicity of these drugs, with only a few pointing to low potential for DNA damage by CQ in tests performed *in vitro* (Ricchio et al. 2001).

Considering the urgency of conducting clinical research that results in safe and effective protocols for the therapeutic use of CQ and HCQ, this timely review aimed to present and discuss relevant aspects for the prevention of toxicological effects during and after treatment of COVID-19.

Pharmacological, therapeutic, and toxicological properties of chloroquine and hydroxychloroquine

General aspects to be considered for prophylaxis or treatment of COVID-19 using CQ and HCQ are summarized in Figure 1. Figure 1(a) emphasizes the physicochemical properties of chloroquine (CQ) and hydroxychloroquine (HCQ). CQ and HCQ are synthetic antimalarials developed from the bark of cinchona (Rubiaceae), which are soluble in water (HCQ is more soluble because it possesses a hydroxyl group), are rapidly fast absorbed with a long plasma elimination half-life of 900 and 1300 hr, respectively (Kalia and Dutz 2007). This leads to tissue bioaccumulation after chronic treatments (Stokkermans and Trichonas 2019).

The cytochrome P450 complex is responsible for the metabolism of CQ and HCQ in the liver, with approximately 50% of metabolites excreted without modification by the kidneys (Kalia and Dutz 2007). CQ and HCQ may also be transported across the placenta. Both drugs were detected in breast milk (Rainsford et al. 2015).

To be successful in replication, viruses need a host intracellular medium with a stable acidic pH in endosomes, lysosomes, and Golgi complex. The antiviral properties of CQ and HCQ are attributed to the accumulation of aminoquinolines that raise the pH of the medium in lysosomes and other intracellular acidic compartments and organelles (Plantone and Koudriavtseva 2018).

It is important to emphasize that treatment of COVID-19 consists not only of inhibiting the viral

replication of SARS-CoV-2, but also of controlling inflammatory processes by reducing the production of pro-inflammatory cytokines and other mediators (Al-Bari and Alim 2017).

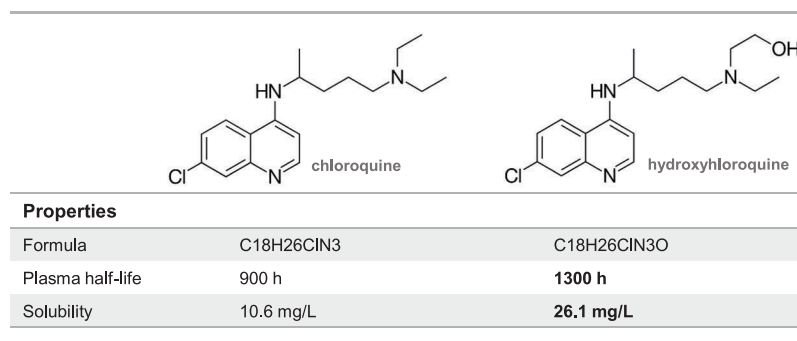
Regarding side effects, the main toxicological outcomes initiated by CQ and HCQ reported in the medical-scientific literature are related to retinopathy, neuromyopathy, and cardiomyopathy. In the retinal pigment epithelium, CQ and HCQ have an affinity for the melanin molecules, producing effects on macular cones (outside of the fovea). More specifically, the retinal pigmented cells react to the accumulation of external segments of the photoreceptors triggered by CQ and HCQ resulting in a decrease in phagocytic activity of lysosomes on the external segments of the photoreceptor, migrating to central and peripheral regions of the tissue and inducing epithelial atrophy with irreversible changes in its photoreceptors (Yam and Kwok 2006).

As mentioned previously due to the long plasma elimination half-life of CQ and HCQ, these drugs are slowly excreted. Thus, even after treatment is stopped, it is necessary to monitor side effects, since pruritus to corneal deposition (keratopathy) and continued maculopathy on the retina may be delayed in occurrence.

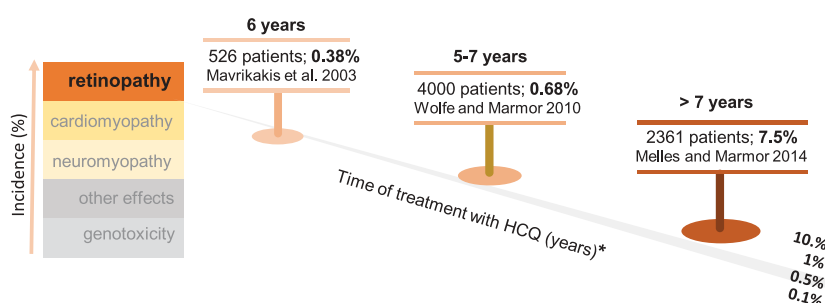
Regarding the occurrence of cardiomyopathy and neuromyopathy, the metabolic mechanisms underlying histological damage mediated by HCQ are similar. Because it is a basic compound, in the intracellular medium of muscle tissues, HCQ enters lysosomes by diffusion, since these organelles have acidic pH. Within lysosomes, HCQ is protonated and accumulates, inhibiting the action of lysosomal phospholipases, resulting in vacuolization of cardiac and skeletal muscle cells (Yogasundaram et al. 2014).

Liu et al. (2018) performed a meta-analysis to investigate the effects of using CQ and HCQ in 16,679 (pooled) patients with rheumatic diseases, but their effects on the cardiomyopathy and neuromyopathy were not confirmed. Chatre et al. (2018) examined cardiac complications attributed to CQ and HCQ in a systematic review of the literature and noted that CQ- or HCQ-related cardiac disorders were rare but severe adverse events occurred after long-term administration.


a) Physicochemical properties of chloroquine (CQ) and hydroxychloroquine (HCQ)




b) Incidence of side effects in patients on long-term HCQ therapy




c) Prescription of CQ | HCQ and patient-care in treatment of COVID-19



Screening
History of previous (or ongoing) use of CQ | HCQ by patients infected with malaria, amebiasis or patients with chronic diseases.
Asian patients are at a higher risk of developing retinopathy.



Monitoring
Patients **with** or **without** vision problems and cardiovascular disease should be periodically monitored during and after treatment with CQ and HCQ.



Treatment
There are possible drug interactions with Kaolin clay, antacids, ampicillin, cyclosporine and mefloquine.
Cumulative doses above 2.3 mg / kg body weight / day must be considered high risk

Figure 1. Toxicological and epidemiological aspects to be considered for prophylaxis or treatment of COVID-19 using CQ and HCQ. (a) Physicochemical properties of chloroquine (CQ) and hydroxychloroquine (HCQ); (b) Incidence of side effects in patients on long-term HCQ therapy; (c) Prescription of CQ | HCQ and patient-care in treatment of COVID-19.

Figure 1B. * In all studies the most important predictor of hydroxychloroquine retinal toxicity was the duration of use (cumulative dose).

Epidemiology of CQ and HCQ retinal toxicity

While controlled clinical studies are still lacking to epidemiologically clarify the incidence of cardiomyopathy and neuromyopathy, the toxicity produced in retinal cells was more comprehensively explored (Melles and Marmor 2014). As shown in Figure 1(b), the incidence of CQ and HCQ retinal

toxicity increases with chronic treatment, which reinforces the hypothesis of bioaccumulation. Considering that the daily doses of CQ and HCQ prescribed vary around 400 mg, after 7 years of treatment, the patient will have received 1 kg of the drug.

Although most investigators found the incidence of retinopathy lower than 2% (Mavrikakis

et al. 2003), two aspects need to be considered when using CQ and HCQ to treat COVID-19: (1) it is a pandemic and, therefore, millions of people will receive treatment and, (2) the doses used in an acute approach to viral infection are often much higher when compared to utilization of CQ and HCQ for treatment of chronic rheumatic diseases (Touret de Lamballerie 2020). In addition, another very important epidemiological consideration is the fact that retinopathy is more common in Asian patients (Melles and Marmor 2015).

Prescription of CQ, HCQ, and patient-care

From the analysis of results obtained in research that investigated the risks of toxicity associated with the use of CQ and HCQ (Castrejón et al. 2014; Gossec et al. 2019), it is evident that some care needs to be considered when prescribing CQ and/or HCQ in treatment of COVID-19, such that side effects are prevented or reduced (Figure 1(c)). Thus, the main challenge is to consider as many epidemiological and clinical aspects as possible before starting treatment.

In this sense, it is important to know the history of previous (or ongoing) use of CQ and HCQ in patients infected with malaria, amebiasis, or individuals with chronic diseases as rheumatoid arthritis and systemic lupus. It is also relevant to remember that Asian patients are at a higher risk of developing retinopathy. Patients with or without vision problems or cardiovascular diseases need to be periodically monitored during and after treatment with CQ and HCQ. It is possible to perform simple tests to measure central and peripheral visual acuity. In addition, symptoms such as ocular pruritus and early signs of cardiac arrhythmias need to be identified.

As for possible drug interactions, the scientific literature describes that Kaolin clay and antacids interact with CQ and HCQ, which may reduce antiviral and anti-inflammatory activity. On the other hand, CQ and HCQ diminish the activity of antibiotics and immunosuppressants, such as ampicillin and cyclosporin. Patients who are being treated with mefloquine are at increased risk of convulsions.

Current recommendations emphasized the fact that toxicity is related to the dose calculated by real weight. Hence, the prescription of daily doses of CQ and HCQ needs to be suitable for patients who are at high risk of presenting adverse effects, considering that cumulative doses above 2.3 mg/kg body weight/day are considered high risk (Marmor et al. 2016).

There is no evidence that the use of CQ and HCQ has a preventive effect on the effects of COVID-19. Thus, clear information regarding the risk/benefit ratio of CQ and HCQ prescription needs to be shared among health professionals and extended to patients and the population. While researchers around the world are looking to develop target-specific drugs against the SARS-CoV-2 virus, current approaches need to be grounded in practices of patient care minimizing risk by rigorous screening and measuring of doses.

Acknowledgments

Financial support is acknowledged to “Coordenação de Aperfeiçoamento de Pessoal de Nível Superior” (CAPES).

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