International Journal of Risk & Safety in Medicine 31 (2020) 111–116
DOI 10.3233/JRS-200024
IOS Press

Article Commentary

Risk of using hydroxychloroquine as a treatment of COVID-19

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Received 14 April 2020
Accepted 19 May 2020

Abstract. The emerging COVID-19 pandemic poses a threat to the global health care system. Given the lack of antiviral therapies or vaccines for the disease, the antimalarial drug hydroxychloroquine (HCQ) obtained much attention as a treatment for COVID-19. However, there are limited and uncertain clinical data to support the beneficial effect of this drug in COVID-19 treatment. HCQ has several side effects and warnings, including blindness, heart failure, and renal toxicity, even with recommended doses. For severe cases of COVID-19 or in patients with preexisting conditions, administering such a drug could be fatal, particularly when taken at high doses or in combination with other antibiotics. However, further well-designed studies that would address the optimal dose, duration of treatment, possible side effects, and long-term usage outcomes are needed to make the final decision. In this paper, we aim to discuss the risk of using HCQ in treating COVID-19 patients, including its possible side effects.

Keywords: Hydroxychloroquine, COVID-19

1. Background

The ongoing COVID-19 pandemic represents a significant public health threat to all countries around the globe [1]. As of May 18, 2020, the pandemic infected approximately 4,800,000 people including nearly 317,000 patients who have died. Unfortunately, the numbers keep increasing worldwide, indicating that the peak is far from near and putting the international community on alert that the worst scenarios are possible. COVID-19 is a viral disease caused by a novel coronavirus. Coronaviruses (CoVs) are large, enveloped, positive-sense, single-stranded RNA viruses that can cause diseases in both animals (gastrointestinal illnesses) and humans (respiratory illnesses) [2–5]. They belong to the order *Nidovirales*, family *Coronaviridae* and the subfamily *Coronovirinae* that contains four genera of CoVs (*Alpha-*, *Beta-*, *Gamma*, and *Deltacoronavirus*) [4]. In rare cases, zoonotic CoVs can mutate and host jump to infect humans, which is what happened in the case of the COVID-19 pandemic. The COVID-19 virus

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originated in bats and transmitted to humans most probably through pangolin in the Wuhan seafood market, China, in December 2019 [6–8]. Genomic analyses revealed that the COVID-19 virus belongs to the *Betacoronavirus* group, the same group that contains the 2003 severe acute respiratory syndrome coronavirus (SARS-CoV). For the similarity, it was named SARS-CoV 2 [9].

Currently, there are no specific antiviral treatments or vaccines available for COVID-19. Treatments mainly focus on symptomatic and respiratory support in life-threatening situations. Passive immunization through plasma transfer from recovered patients might be an option as a rescue strategy [10–12]. Given the lack of registered clinical therapies or vaccines, many physicians and scientists examine previously used clinical drugs for COVID-19 treatment [13–16]. Even though these drugs are not registered as antiviral drugs for SARS-CoV 2, they are implemented because the infection is uncontrollable at this point. Although many drugs have been reported to show promising results against SARS-CoV 2, none of them gained as much attention as the antimalarial drugs chloroquine (CQ) and analog hydroxychloroquine (HCQ) [14,17,18].

CQ and HCQ are antimalarial drugs that were produced in the 1950s. HCQ is a chloroquine analog found to be more potent than CQ and has the same mechanism of action, but has a safer profile, which makes it the prioritized drug [19]. Later on, HCQ was used to treat autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [20]. In the wake of COVID-19, a few studies reported antiviral activity of HCQ against SARS-CoV-2 [14,17,18]. Following the promising results of these first clinical trials, doctors around the globe incorporated the usage of HCQ for certain COVID-19 patients under specific conditions. However, HCQ is well known to have severe complications and side effects in some cases. There is a higher risk of adverse effects using HCQ in people with preexistence conditions; the same people COVID-19 is killing. This is particularly the case when taken at high doses or in combination with other antibiotics. Therefore, in this paper, we aim to discuss the mechanism of HCQ action as a drug, how it could affect the SARS-CoV 2 infectious cycle, and the risk of using HCQ for COVID-19 treatment.

1.1. Hydroxyquinolone as a potential mechanism of action against SARS-CoV 2

SARS-CoV 2 is transmitted from human-to-human through droplets inhalation or direct contact, even though the fecal-oral route might also be possible. It primarily infects ciliated bronchial epithelial cells and type II pneumocytes, where it binds to the surface receptor, angiotensin-converting enzyme 2 (ACE2), through S glycoprotein that is found on its surface [21–24]. Binding of the viral S glycoprotein and ACE2 mediates viral entry to the cell through endocytosis. In a cell-membrane derived vesicle called an endosome acidity plays an essential role for its maturation [25].

There are several potential molecular mechanisms of action of HCQ against SARS-CoV-2 that have been postulated [14,17,18,26]. Generally, HCQ is a weak base drug that accumulates in the cell acidic compartments such as lysosomes and endosomes. This accumulation increases the pH and inhibits the maturation of these endosomal compartments. HCQ might prevent the endocytosis of SARS-CoV-2 by raising the pH level of the endosome, which would block the virus entry and exit from host cells [14,17,18]. On the other hand, HCQ might reduce glycosylation of ACE2, interfering with SARS-CoV-2 to bind effectively to the host cell [27]. Furthermore, a recent publication hypothesizes that HCQ reduces the production of pro-inflammatory cytokines (such as interleukin-6, IFN-alpha, and TNF), thereby inhibiting various immune pathways that might lead to acute respiratory distress syndrome (ARDS) [20].

1.2. Clinical use of hydroxyquinolone for COVID-19 treatment

Currently, the empirical evidence for HCQ effectiveness in COVID-19 is limited. The first report of clinical use of CQ came out of China in February 2020, revealing that 100 COVID-19 patients treated with CQ showed significant improvements of pneumonia and lung imaging and reduction of the duration of illness without any adverse effects [26]. However, the findings of this research have never been published. On the other hand, the first clinical trial data of using HCQ were published by Gautret et al. in France on 17 March 2020 [18]. The trial included 36 patients diagnosed with SARS-CoV-2 and divided 20 patients in the treatment group and 16 patients in the control group. The treatment group received HCQ 200 mg for ten days, three times a day (600 mg daily). In order to prevent bacterial infection, six patients out of the treatment were also prescribed azithromycin. On day 6, PCR testing of the treatment group showed a significant reduction in the viral load in comparison to the control group. Furthermore, the six patients who received a combination of HCQ and azithromycin were tested negative, which indicates the high effectiveness of the combination. Following the promising results of this clinical trial, every health care system recommended incorporating HQC in their treatment strategy for 10 days. In addition, the U.S. Food and Drug Administration (FDA) in the USA approved the careful use of HCQ under an Emergency Use Authorization (EUA). Even though FDA did not approve HCQ as either safe or effective to treat or prevent COVID-19, many used the FDA-approved label for marketing and recommended the use of HCQ [28].

Although promising, besides the trial by Gautret et al., there are no data from any other trials that demonstrated the effectiveness of HCQ for COVID-19 treatment. The French trial also has some limitations. They used a sample size of 36, which is small. In addition, results indicated that one of the patients who tested negative on day 6 had tested positive on day 8. Such recurrences imply the need for long-term research before assessment of the effectiveness of HCQ. Given these limitations, and despite the fact that HCQ is being used for nearly one month at the moment of writing, one can conclude that there is no apparent success of using HCQ for COVID-19 treatment.

1.3. Hydroxyquinolone dosage and side effects

HCQ has a well-established safety profile since it has been in clinical use for many years. Reports from various studies and the drug label are very clear about risks and warnings of HCQ usage. The most common side effect of HCQ usage is gastrointestinal upset [20,29]. Cardiotoxic effects have been reported as well, including cardiomyopathy and heart rhythm disorders, where HCQ was found to cause electrical disturbance in the heart [30–32]. In severe cases, retinopathy has been reported with the possibility of blindness due to retinal damage [33–35]. Other potential side effects include loss of consciousness due to low blood sugar, suicidal behavior, heart failure, and potentially lethal interactions with other drugs [32,36,37]. Furthermore, HCQ metabolism takes place in the liver with a renal clearance of some metabolites. Doctors should take care when prescribing HCQ for patients with liver or renal problems [20]. There are reports that raise concerns of SARS-CoV 2 causing liver and renal impairment, using HCQ for COVID-19 treatment might increase the risk of toxicity [38].

Typically, the suggested dose for HCQ to treat malaria in adults is 800 mg orally as an initial dose, followed by 400 mg at 6, 24, and 48 hours after the initial dose, a total of 2000 mg over three days (Hydroxychloroquine Sulfate Fact Sheet for Patients - U.S. Food and Drug Administration (FDA)). The optimal dosing and duration of treatment for COVID-19 are unknown. However, there are recommendations from health care authorities. The FDA has issued an Emergency Use Authorization (EUA) of HCQ and suggested the following dose and duration: 800 mg of hydroxychloroquine sulfate on the first day of

treatment and then 400 mg daily for four to seven days of total treatment based on clinical evaluation. On the other hand, The CDC panel did not recommend using a high dosage of the drug (i.e. 600 mg twice daily for ten days), because increasing the dose may have unwanted adverse outcomes that should be carefully monitored.

Despite these warnings, many clinical trials currently investigate the effectiveness of CQ or HCQ in treating COVID-19 using higher doses than those recommended for the authorised indications. Some concerns of the CDC have been confirmed by a randomized clinical trial from Brazil, where the physicians noticed arrhythmia within two to three days in patients who received the high dose, i.e. 600 mg CQ twice daily for ten days. On the sixth day of the trial, 11 patients died and the second phase was stopped immediately [39]. The study's findings suggest that a high dose of CQ (and consequently HCQ) causes heart rhythm problems. These problems could be intensified if treatment is combined with azithromycin, which has similar effects on the heart.

2. Conclusions

HCQ is originally an antimalarial drug that has been used for the treatment of patients with rheumatic diseases as well. Although it has been in clinical use for many years, its mechanism of action is still on the rise. Previous studies have shown that HCQ is effective against several viruses. Potential antiviral activity of HCQ could be carried out through alkalization of the cellular phagolysosome, which interferes with pH-dependent steps of viral replication. In the wake of COVID-19, a few studies reported that HCQ showed antiviral activity against SARS-CoV-2. Given the lack of antiviral therapies or vaccines, it was approved as a potential intervention strategy for COVID-19 treatment. However, HCQ has several side effects and warnings, including blindness, heart failure, and renal toxicity, particularly when taken in higher doses. These potential side effects are worrisome in the case of COVID-19 for different reasons. Firstly, we do not know what the dosage or the duration of the treatment are. Secondly, many COVID-19 patients already have underlying health conditions, so higher doses of HCQ could be fatal. Despite the initial optimism of using HCQ, there is growing skepticism about its effectiveness in treating COVID-19 at this point. However, there are tens of on ongoing clinical trials of HCQ efficacy and so it takes time to tell the final word.

Conflict of interest

The authors declare no conflict of interest.

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