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Physiological impact of some drugs to control COVID-19 pandemic: Literature Review

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Abstract

Coronavirus is the cause of the widely distributed endemic disease COVID-19 that has turned into a global disaster. Choosing the safe and effective therapy is the most effective problem in treating the disease and reducing the total number of death. The presentation of initial treatment must be reliable with the ethics of medicine. This review study aims to focus on the pharmacokinetic features of Hydroxychloroquine (HCQ), Chloroquine (CQ), and Ivermectin (IVM) to prevent the transmission and development of COVID-19 and lower its mortality rate. HCQ, CQ, and IVM have been used as therapeutics for COVID-19. Chloroquine and hydroxychloroquine share similar chemical structures and mechanisms of action. They are used commonly for anti-parasitic, anti-inflammatory, lysosomotropic properties**,** antiviral effects, and several chronic diseases such as systemic lupus erythematosus plus rheumatoid arthritis with common adverse effects. These preparations can affect many cellular pathways for the replication and transcription of the biological virus, including enterovirus, Zika Virus, yellow fever, and avian influenza. These remedies are manufactured in tablets form for oral administration. Ivermectin is a class of drug and is commonly used to treat scabies and lice. Hydroxychloroquine and ivermectin were known to act by generating an acidic atmosphere.

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Introduction

Viral diseases are the most contagious infectious diseases and are common for establishing major biological, clinical, and socioeconomic difficulties (Meo *et al*., 2020). COVID-19, also known as 2019-nCoV, belongs to the family Coronaviridae of the genus Betacoronavirus. This virus is created as an animal infection and eventually transmitted to humans (W H O, 2020 A). Various therapeutic strategies have been tried for the COVID-19 treatment, including antiviral, antibacterial, and glucocorticoid drugs. The two antimalarial drugs,

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Chloroquine (CQ) and hydroxychloroquine (HCQ), were used for the treatment of SARS-CoV-2 activity (Gautret *et al.,* 2020) also for autoimmune diseases, specifically systemic lupus erythematosus and rheumatoid arthritis **(**Perricone *et al.,* 2020). Several studies have been reported the chloroquine and hydroxychloroquine efficacy and safety. Chloroquine [7-chloro-4-(4-diethylamino-1- methyl butyl amino) quinoline, CHQ] is a prevalent drug for treating malaria in many Third World countries. It is cheap, broadly available, relatively well-tolerated, and has quick action inception. Chloroquine and hydroxychloroquine are 4-aminoquinoline synthetics derived from the bark of cinchona Quinine (Srinivasa *et al.,* 2017). Additionally, both compounds are soluble in water and are weakly alkaline, and after entering the cell, they prompt a pH surge in acidic organelles.

Moreover, the raising in the intracellular pH has been shown to block viral infections (Legssyer *et al.,* 2003) due to solid immunomodulatory ability (Lee *et al.,* 2011) plus its safety as therapy for COVID-19 disease (Putra *et al.,* 2020). Ivermectin was discovered earlier from *Streptomyces avermectinius in* 1967 (Juarez *et al.,* 2018). It is insoluble and unstable in water solubility (Eerike *et al.,* 2022). In the 1970s, ivermectin was developed as a new class of drug used to treat scabies and lice. At the beginning of its discovery, ivermectin was used in veterinary medicine, and it was noted to be non-toxic and effective in humans. Ivermectin is used as stimuli in treating Onchocerciasis and Lymphatic filariasis (Crump and Omura, 2011). It has been extensively used in dogs as a heartworm protective (Hopper *et al.,* 2002).

It is worth mentioning that Chloroquine has been used for more than 70 years, and it's an atypical list of critical medicine (Colson *et al.,* 2020). These drugs are considered potential "game-changers" in the popular media for COVID-19. The favorable schedule for the treatment of COVID-19 founded on this modeling was a primary dose of 400mg hydroxychloroquine and a care dose of 200mg (Yao *et al.,* 2020)**.** The mechanism of action of Chloroquine was first studied in SARS-CoV by inhibiting virus replication in a Vero cell model (Vincent *et al.,* 2005; Biot *et al .,* 2006) also are capable of affecting several cellular paths (Okafor *et al.,* 2020). The current review study intends to focus on the pharmacokinetic features of Hydroxychloroquine (HCQ), Chloroquine (CQ), and Ivermectin (IVM) to prevent the transmission and development of COVID-19 and lower its mortality rate.

Pharmacokinetics and mechanism actions

Chloroquine was first synthesized in 1934 (Tönnesmann *et al.,* 2013). The sulfate and phosphate salts of Chloroquine have both been commercialized as antimalarial drugs. Chloroquine interferes with the glycosylation process, plus it inhibits the function of endocytosis in the intermediate phase and virion transport. However, Chloroquine stops viral protein production (Savarino *et al.,* 2003). While, ivermectin suppresses the replication of RNA viruses with a single dose and switches a viral non-structural protein (Nsp7) responsible for replicating the viral genome (Patrì & Fabbrocini, 2020; Smith *et al .,* 2020; Dasgupta *et al.,* 2020). Also, this drug interferes with nematode fertility by inhibiting the microfilariae formation in utero **(**Laing & Devaney, 2017).

As therapeutics for malaria

Malaria is one of the most prevalent parasitic diseases in the world. It affects approximately 500 million individuals throughout developing countries' tropical and subtropical areas. It causes considerable morbidity and mortality, with about 800,000 deaths worldwide each year (WHO, 2010); HCQ/CQ has been extensively studied and widely used to prevent and treat malaria for many decades (Das *et al.,* 2020). These drugs treated malaria in the 17th century (Achan *et al.,* 2011)**.** Due to the insufficient supply of quinine in the early 19th century, CQ was synthesized as a candidate substitution for quine as an anti-malaria drug in the 1930s (Kasim, 2019). In the 1940s, CQ was subsequently resynthesized by introducing a hydroxyl group named HCQ, and this defined compound was more active but less toxic than CQ (Slater, 1993). The malarial pathogen attacks red blood cells, lysis the RBCs, and degrades the hemoglobin into the vacuoles of the parasitic cell. It acquires those amino acids for constructing its proteins and energy metabolism (Khuroo *et al.,* 2020). CQ is a lysosomotropic agent and crosses plasma membrane and organelle membranes CHQ also inhibits cytokine release into the blood, an effect that could be beneficial in diseases related to bacterial-induced inflammation (Karres *et al.,* 1998). Today, the CQ is known to be effective against malarial parasites of the Plasmodium genus, like Plasmodium malariae, Plasmodium ovale, and Plasmodium vivax. However, it is not effective against Plasmodium falciparum, owing to the resistance developed (Mejia *et al.,* 2013). These parasites can survive in major insect vectors of malaria and trypanosomiasis
(Pooda *et al.,* 2014).

Antiviral effects

Chloroquine is one of the effective drugs in preventing the distribution of SARS CoV in cell culture. Moreover, the favorable inhibition of the spreading of the virus was observed when the cells were either treated with Chloroquine before or after SARS CoV infection (Vincent *et al.,* 2005).
In vitro experiments revealed that CQ and HCQ can inhibit the growth of a variety of viruses, including human coronavirus, enterovirus, Zika Virus and Influenza A (Tan *et al.,* 2018) and Hepatitis C (Picot, 2020), Borna disease virus, and the Avian leucosis virus (Savarino *et al.,* 2003). CQ inhibits the quinone reductase-2, which is involved in sialic acid biosynthesis required for ligand recognition. The potency of CQ can be increased when used with a cell antiviral agent (Al-Bari, 2020). Previous studies found that CQ and HCQ exert antiviral effects through multiple mechanisms. Moreover, raising the intracellular pH has been shown to block viral infections (Legssyer *et al.,* 2003). However, to obtain an equivalent antiviral effect, a higher concentration of Chloroquine was needed if the medication was added 3 or 5 h after adsorption **(** Vincent *et al.,* 2005**)**. Ivermectin is being examined in the context of treatment of several infectious diseases, including Zika virus, dengue virus (DENV), yellow fever, avian influenza, porcine reproductive and respiratory syndrome, and HIV Type 1 (Arévalo *et al.,* 2020). Hydroxychloroquine and ivermectin were known to

create the acidic environment and inhibit the importin (IMPα/β1) mediated viral import. Ivermectin suppresses the replication of several RNA viruses with a single dose of the drug able to control viral replication within 24 to 48 hours (Patrì & Fabbrocini, 2020).

Toxicity

In 1955, the HCQ was approved for the first time, with a favorable efficacy and reduced toxicity, compared to CQ (Ben-Zvi *et al.,* 2012). Despite this, the toxicity of HCQ is well documented, and adverse side effects may have significant future uses associated with its lysosomotropic and immunomodulatory mechanisms (Kalra *et al.,* 2020). Gautret *et al.,* (2020) was studied the clinical trials and the toxicity profile of CQ or HCQ in combination with azithromycin. Clinical experience has shown that Chloroquine was well absorbed in the body and distributed widely in the bloodstream. It has an apparent and terminal half-life of 6 days and two weeks (Smit *et al.,* 2020). Cytochrome P450 metabolizes the drug, and renal clearance is responsible for one-third of the total clearance of Chloroquine (Knights *et al.,* 2013). Therefore, it is probable that Chloroquine can be used safely for an acute virus infection in the lower dose. Still, some of the potential side effects of HCQ and CQ, such as vomiting, diarrhea and increased risk of arrhythmia, should also be taken into account (Singh & Vijayan, 2020). CHQ is an effective autophagic drug that may lead to cellular degradation of hepatocytes in the liver with the concurrent production of vacuoles (Cooper & Magwere, 2008). Remarkably, the daily a and duration of use are the main risk factors; when the HCQ amount exceeds 20 mg/kg, the incidence of retinopathy is 25 to 40% within 1 to 2 years (Marmor *et al.,* 2016). that two-dose ivermectin prophylaxis at a dose of 300 µg/kg body weight with a gap of 72 hours was associated with a 73% reduction of COVID-19 **(**Behera *et al.,* 2020).

Although the duration of HCQ and CQ treatment in COVID-19 patients is generally concise, it is still necessary to be aware of their retinal toxicity. Retinal degeneration caused by HCQ and CQ can develop even after treatment is stopped. CQ and HCQ affect the cardiac conduction system; their use should be avoided in combination with other drugs that block cardiac conduction to prevent fatal arrhythmia, among them, digitalis drugs antiarrhythmic drugs (Touret de Lamballerie., 2020). Both HCQ and CQ are mainly metabolized via the liver and kidney and have long half-lives (approximately 1-2 months) (Plantone & Koudriavtseva, 2018). Therefore, long-term monitoring for their renal and hepatotoxicity is necessary. Importantly, recent reviews and meta-analysis indicate that high dose ivermectin has comparable safety as the standard low-dose treatment, although there is not enough evidence to make conclusions about the safety profile in pregnancy (Navarro *et al.,* 2020; Nicolas *et al.,* 2020).

Potential treatment of COVID-19

Chloroquine is a relatively safe, effective, and cheap drug used for treating many human diseases, including malaria, amoebiosis, and human immunodeficiency virus. It effectively inhibits the infection and spread of SARS CoV-2 in cell

culture (Vincent *et al.,* 2005). HCQ and CQ were found to have exerted anti-SARS-CoV-2 effects both in vitro and in vivo and represent potential treatment options for COVID-19 (Zou *et al.,* 2020). In March 2020, the WHO stated that COVID-19 virus infection became a global pandemic in many countries worldwide (WHO, 2020 B). Chloroquine (CQ) and hydroxychloroquine (HCQ) are already being used off-label to treat COVID-19 in many countries (Touret & de Lamballerie, 2020). This is all true of Chloroquine and hydroxychloroquine, both 4-aminoquinolines, suggested as potential treatments for covid-19 (Ferner & Aronson, 2020)**.** Health care providers should be aware that CQ or HCQ at high doses could be toxic and life-threatening. One randomized controlled trial using HCQ for treatment of COVID-19 was conducted in Wuhan, China, and the results showed that HCQ treatment meliorated the fever and reduced the cough duration (Chen *et al.,* 2020). More importantly, more clinical studies with critically ill COVID-19 patients demonstrated that HCQ even could significantly minimize death risk without apparent side effects (Yu *et al.,* 2020).
Moreover, ivermectin may reduce the risk of death in the treatment of covid-19 by preventing transmission and development of COVID-19 disease in those exposed to infected patients (Behera *et al.,* 2020). Ivermectin could block a viral non-structural protein (Nsp7) responsible for the replication and transcription of the viral genome (Dasgupta *et al.,* 2020)**.** The more commonly used combined therapy with Ivermectin-Azithromycin-Cholecalciferol given for 7days was effective in reducing symptomatology duration and clinical progression of COVID-19 (Espitia-Hernandez *et al.,* 2020).

Conclusion

To date, very few treatments have been demonstrated to reduce the burden of morbidity and mortality from covid-19**.** The absence of effective therapy against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has led clinicians to redirect drugs that are known to be effective for other medical conditions to the treatment of COVID-19. Although CQ, HCQ, or ivermectin revealed a favorable safety profile, the tested drugs do not reduce the need for supplemental oxygen, ICU admission, invasive ventilation, or death in patients hospitalized with a severe form of COVID. HCQ is one of the most successful and widely used medications and with obvious health precautions, saving countless lives from the scourge of malaria. Its relatively simple manufacturing methods mean that it is affordable in many countries worldwide. Even though the benefits of Chloroquine and hydroxychloroquine for COVID-19 therapy are still limited to small clinical trials with poor methodology, unmeasurable outcomes, non-randomized and open-label, their use can still be considered by assessing the benefits and risks to patients, consider examining the early signs of cardiac arrhythmia before giving the therapy to patients with COVID-19 infection. The other things to consider are the presence of risk factors that can be precipitated the heart.

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