Abstract. – Chloroquine, a 4-aminoquinoline derivative, was initially used to treat malaria. It was later found to have immunomodulating, anti-infective, anti-thrombotic, anti-tumor, and metabolic effects. Recently, many studies have focused on the application of chloroquine in viral infections. Most in vitro studies suggested that chloroquine exerted some benefit in infections from viruses. However, animal experiment and clinical trials that attempted to use chloroquine in prevention or treatment of viral infections have reported disappointing results. It might be attributable to inadequate steady-state whole blood chloroquine concentration necessary for exerting its antiviral effects. A 16 μM/L steady-state whole blood concentration of chloroquine should suffice in antiviral treatment with minimal toxicity. Furthermore, chloroquine has both acute and cumulative toxicity. Hence, not only the appropriate treatment dose is crucial, the occurrence of adverse reactions should also be closely monitored and treated in time. Herein, we report the antiviral mechanisms, effects, safety and adverse effects of chloroquine.

Key Words: Chloroquine, Antiviral mechanisms, Antiviral effects, Safety, Adverse effects, COVID-19.

Introduction

At the end of 2019, a Novel Coronavirus (SARS-CoV-2) broke out in Wuhan of China. This brand-new virus can cause pneumonia and other complications, including acute respiratory distress syndrome, acute kidney injury, cardiac injury, liver dysfunction, hyperglycemia, gastrointestinal hemorrhage, pneumothorax, urinary tract infection, etc¹. Still no specific vaccine or drugs have been found for its prevention or treatment. In the context of this pandemic, the multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province of China announced an expert consensus on chloroquine phosphate for the treatment of Novel Coronavirus pneumonia. The expert consensus recommended that chloroquine should be used in the treatment of Coronavirus disease 2019 (COVID-19)².

Chloroquine (CQ) is a veteran drug, which was first synthesized by Hans Andersag through modification of quinine structure, and was originally used for the treatment of malaria³. During World War II, malaria-infected soldiers who were treated with CQ had significant improvement of rashes and arthritis. Hence the immunomodulating activity of CQ was found and it was gradually used in autoimmune diseases⁴. However, the exact mechanism for the action of CQ is not fully understood.

Widely accepted mechanisms at present include interfering with DNA functions, inhibiting prostaglandin formation, inhibiting the chemotaxis and phagocytic effects of polymorphonuclear cells, and regulating the release of cytokines⁵. Hydroxychloroquine (HCQ) is an analogue of CQ and has a similar mechanism of action to CQ. With continuous studies on CQ and its analogue HCQ, more therapeutic properties have been discovered, which can be summarized as immune regulation, anti-infection (including anti-parasite, anti-bacterial, anti-fungal and anti-viral), anti-thrombotic, anti-tumor and metabolic effects⁶. The outbreak of novel coronavirus disease has raised concerns about the antiviral effect of CQ. This paper will focus on the antiviral mechanisms, effects, safety and adverse effects of CQ.

Antiviral Mechanisms

Inhibition of Viral Infection

When a virus enters the body, viral attachment protein binds to the specific receptor on the plas-
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tissue membrane of susceptible cells, such as tissue
macrophages, monocytes, dendritic cells, endo-
thelial cells, and hepatocytes. Then, virions can
be internalized into vesicles which traffic through
the way of pinocytosis, fusion, and penetration.
After the acidification and cleavage of viral gly-
coproteins in acidic lysosomes (pH ~5.5), the vi-
rus can start to replicate under several enzymes.
Without acidification and cleavage, the infection
is abrogated. CQ is a synthetic 4-aminoquinone-
line derivative and a weak base. On oral adminis-
tration, CQ is readily absorbed and concentrated
in tissues, such as the liver, spleen, kidney, and
lung. Once in the cells, CQ becomes protonated
and concentrated in acidic organelles, such as the
endosomes and Golgi vesicles. As a weak base,
CQ, then, destroys the structure and function of
these acidic organelles by increasing PH, result-
ing in inhibition of virus infection and replication.
The known mechanisms include: (1) interferring
with endocytosis and blocking viral entry in cells;
(2) inhibiting the activity of several proteases and
interfering with the proteolytic process; (3) inhib-
itating the activity of protein-modifying enzymes,
thus changing the process of viral protein modi-
fication to reduce or inactivate the ability of viral
infection; (4) disfunction the late endosomes and
inhibiting viral assembling and budding from the
infected cells. Furthermore, CQ can also inter-
fere with DNA replication and gene expression
to exert viral inhibition by inhibiting transferrin
from releasing iron ions and reducing the iron
content in cells.

Reducing the Damage of Inflammatory
Response

Mostly in the final stage of the viral infections,
a cytokine storm may be induced by the overacti-
vated immune system. The cytokine storm might
then cause acute respiratory distress syndrome and
multiple organ failure in such extreme immu-
ne attack. CQ and HCQ can inhibit immune overactivation in different ways: (1) increasing the
PH value of intracellular compartments of an-
tigen presentation cells and interfering with the
function of phagocytosis and antigen presenting;
(2) preventing the T cells activation, proliferation
and inhibiting the expression of co-stimulation
molecules on account of less antigen presenting,
thus decreasing the release of several pro-inflam-
mation factors, including interferon-γ, tumor ne-
crosis factor (TNF), interleukin (IL)-1, IL-6 and
IL-2; (3) blocking the interaction of Toll-like re-
ceptors (TLRs) with ligands, and inhibiting its
mediated cellular activation and cytokine produc-
tion. Therefore, CQ and HCQ may delay or con-
tain the deterioration of diseases by blocking the
generation of cytokine storms.

Anticoagulation and Antithrombosis

Respiratory virus infection can cause acute
lung injury by inducing abnormalities in the clot-
ting system. Infection of severe influenza A
virus can induce abnormal activation of the pul-
monary epithelial cells. The activated pulmonary
epithelial cells can release tissue factors into the
blood to activate the endogenous coagulation
pathway and lead to platelet aggregation and
thrombosis. Highly pathogenic coronaviruses,
i.e. severe acute respiratory syndrome corona-
virus (SARS-CoV), the Middle East respirato-
ry syndrome coronavirus (MERS-CoV) and the
novel coronavirus (SARS-CoV 2), induce blood
coagulation dysfunction and high level of inflam-
matory factors. Increasing expression of in-
flamatory cytokines may enhance coagulation
cascade and break the physiological balance of
the blood coagulation and fibrinolysis, which may
induce hypercoagulable state and promote throm-
bosis. Post-mortem examination of 20 patients
confirmed with SARS in 2003 in Toronto, Cana-
da showed that in addition to predominant diffuse
alveolar damage and acute fibrinous organizing
pneumonia, the pathological features of SARS-
lung still included vascular endothelial damage of
both small-sized and mid-sized pulmonary ves-
sels and vascular fibrin thrombi, which were often
associated with pulmonary infarcts.

CQ and HCQ can prevent thrombosis by inhib-
itating the release of inflammatory factors, reduc-
ing red blood cell aggregation, inhibiting platelet
aggregation and adhesion, reducing blood viscos-
ity, and enhancing antiplatelet activity. HCQ has
been shown to prevent significant thromboem-
bolic events after total hip replacement or during
pregnancy. Whether CQ and HCQ can play a
positive role in preventing hypercoagulable state
and thromboembolic risk in coronavirus infection
remains to be confirmed.

Antiviral Effects of Chloroquine

HIV

As early as 1993, HCQ was found to inhibit
the replication of human immunodeficiency vi-
rus (HIV) in primary T cells and monocytes.
CQ can change the glycosylation pattern of the
HIV-1 gp120 envelope, inhibit HIV replication in CD4+ T cells, inhibit transactivation of the HIV-1 long terminal repeat and induce the selective apoptosis of the memory T cell compartment (CD45RA–CD45RO+) in vitro. Two clinical trials conducted by Sperber et al in 1995 and 1997 demonstrated the anti-vehicular effect of HCQ on HIV-1. Subsequent clinical trials suggested that HCQ showed no effect when given alone in HIV patients but synergistically acted when combined with other antiretroviral drugs. Furthermore, using CQ in HIV positive pregnancy women is associated with a decreased rate of vertical transmission of the virus to their infants. However the same dosage of CQ did not show the similar anti-HIV effects in other clinical trials. Some researchers have emphasized on the starting time and dosage selection in order to maximize efficacy of CQ.

**Influenza Virus**

CQ was able to inhibit the replication of influenza virus A in vitro at low concentrations. In vitro, the inhibitory effect was maximal when the drug was given at the time of infection and was lost after 2 h post-infection. This timing approximately corresponded to that of virus/cell fusion and it suggested that CQ may be effective in the prevention of influenza. However, CQ was not as effective as preventive therapy in animal models in vivo. In a randomized, double-blind clinical trial, chloroquine phosphate (500 mg/day for one week, followed by once a week for 12 weeks) had no protection against influenza viruses compared to placebo.

**Dengue Virus**

Farias et al found that CQ inhibited the replication of Dengue virus-2 by increasing the pH value of endosome in Vero cells and U937 cells. CQ could also inhibit the cytotoxic and immune-inducing effects of dengue virus-2. Later, they also confirmed that CQ could interfere with the replication of dengue virus-2 in macaques. A randomized, double-blind clinical trial showed that CQ improved the clinical symptoms of dengue fever patients.

**Ebola Virus**

Ebola virus belongs to filoviruses family, and it is one of the most virulent pathogens, with a mortality rate ranging from 59 to 88%. It has been reported that CQ could interfere with the process of the virus entrance and replication in vitro to inhibit Ebola virus in mice. In 2015, Long et al claimed that CQ could be a candidate for the treatment of Ebola according to their in vitro experimental result. Although CQ has been reported to be ineffective in Ebola patients, the survival rate of infected mice was 80% in a mouse model. Mice were delivered CQ with a dosage of 90 mg/kg body-weight twice daily for 14 days to maintain the stable whole blood concentration of CQ at 2.5 μg/ml. Therefore Akpovwa, considered that negative results of the clinical trials might attribute to the failure of maintaining therapeutic concentration of CQ in plasma.

**Coronary Virus**

In 1984, Krzystyniak et al found that CQ could change the pH value of endosomes to inhibit the entry of mouse hepatitis viruses (Coronaviruses) into cells. In 2003, after the SARS outbreak, Savarino et al proposed that CQ might have an effect on the treatment of SARS. Subsequently, Keyaerts et al of the University of Leuven, Belgium showed that CQ phosphate could inhibit the replication of SARS-CoV in Vero E6 cell line with 50% inhibitory concentration [IC50 = (8.8±1.2) μM], close to the serum CQ concentration during the treatment of acute malaria but significantly lower than its 50% cell inhibitory concentration (cytostatic activity) [CC50=(261.3±14.5) μM], suggesting the safety of CQ in this cell line. In addition, chloroquine was significantly effective even when the drug was administered 3-5 h after infection, suggesting an antiviral effect even after the establishment of infection. Vincent et al from the US Centers for Disease Control and Prevention (CDC) further elucidated that CQ inhibited viral replication by reducing the terminal glycosylation of the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of Vero E6 cells and interfering with the binding of SARS-CoV to ACE2 receptor. Mice experiments proved that CQ could not reduce the viral load in mice infected with SARS-CoV, but it had a certain inhibitory effect on the inflammatory response caused by viral infection. In vitro, it was found that CQ also had a certain inhibitory effect on another Coronavirus, MERS-CoV.

A paper published by Science China Life Sciences on March 2020 found that the SARS-CoV-2 spikes (S) protein was similar to the S protein structure of SARS-CoV, and could also infect host epithelial cells by binding to ACE2 receptor on the surface of host cells via S protein. Moreover, a joint study conducted by the Wuhan In-
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stite of Virology, Chinese Academy of Sciences and the Institute of Toxicology and Pharmacology, Chinese Academy of Military Medical Sciences, showed that Remdesivir (GS-5734) and CQ (Sigma-c6628) could effectively inhibit SARS-CoV-2 at the cellular level.

According to the Diagnosis and Treatment Protocol for COVID-19 (Trial version 7) by National Health Commission of the People’s Republic of China and National Administration of Traditional Chinese Medicine, the clinical sub-types are as follows. (1) Mild type: patients with mild clinical symptoms and no imaging evidence of pneumonia. (2) Moderate type: patients with fever and respiratory symptoms as well as imaging evidence of pneumonia. (3) Severe type: for adults meeting any of the following: i. polypnea (<2 months, respiratory rates (RR) ≥30 times/min; ii. pulse oxygen saturation (SpO₂) ≤93% in a resting state; iii. arterial partial pressure of oxygen (PaO₂)/fraction of inspiration O₂ (FiO₂) ≤ 300 mmHg and for patients in the region of high altitude (≥1000m), the value of PaO₂/FiO₂ should be corrected as following formula: PaO₂/FiO₂ × [Atmosphere(mmHg)/760]. Besides, adult patients with rapidly progress of pulmonary lesions >50% in imaging should be managed as severe type; for children meeting any of the following: i. polypnea (<2 months, respiratory rates (RR) ≥60 times/min; 2-12 months, RR ≥50 times/min; 1-5 years old, RR ≥40 times/min; >5 years old, RR ≥30 times/min) excluding the impact of fever and crying; ii. pulse oxygen saturation (SpO₂) ≤93% in a resting state; ii. signs of accessory respiration (groan, nasal flaring or three concave sign); iv. drowsiness, convulsions; v. antifeedant or feeding difficulty, with dehydration. (4) Critical type: patients meeting any of the following: i. respiratory failure and requiring mechanical ventilation; ii. shock; iii. combining with any other organ dysfunction and requiring ICU management. Expert consensus on chloroquine phosphate for the treatment of Novel Coronavirus pneumonia of China recommends that mild, moderate or severe patients aged between 18 to 65 can be treated with chloroquine phosphate after exclusion of contraindications. A dosage of 500 mg twice a day for 7 days is recommended for patients weighing over 50 kg, while a dosage of 500 mg twice a day for the first 2 days and once a day for the rest of 5 days is recommended for those weighing less than or equal to 50 kg. At present there are 23 clinical trials of CQ for the treatment of COVID-19 in China according to the register information on Chinese Clinical Trial Registry. The contraindications of using chloroquine listed in the consensus included: (1) age <18 years old or age >65 years old; (2) women in pregnancy; (3) documented history of allergy to 4-aminoquinoline compounds; (4) documented history of hematomal system diseases; (5) documented history of chronic liver and kidney diseases, especially at the end stage; (6) documented history of cardiac arrhythmia or chronic heart diseases; (7) documented history of retina or hearing dysfunction; (8) documented history of mental illnesses; (9) documented history of skin disorders (including rashes, dermattis, psoriasis); (10) documented history of deficiency of glucose-6-phosphate dehydrogenase (G6PD); (11) use of any of the medications below due to the previous diseases including primaquine, digitalis, benzodrine, thyrroxine, streptomycin, metronidazole, monoamine oxidase inhibitor, chlorpromazine, triamcinolone, proguanil, mefloquine, phenylbutazone, heparin, penicillamine, aminoglycoside antibiotics. The consensus especially emphasized that to avoid the potential risk of prolonged QT intervals and even torsade de pointes, antibiotics, including respiratory quinolones and macrolides should not be prescribed when patients are undergoing the treatment of CQ. Besides, the serum electrolyte levels (potassium, sodium, chlorine), blood glucose, liver and kidney function are ensured to be normal.

A clinical study to evaluate the efficacy and safety of CQ in hospitalized patients with COVID-19 was initiated in China from January 27, 2020 to February 15, 2020. In this study, patients were randomized into two groups. For experimental group, 10 patients including 3 severe and 7 moderate cases were treated with chloroquine phosphate 500 mg orally twice daily for 10 days. For control group, 12 patients including 5 severe and 7 moderate cases were treated with Lopinavir/Ritonavir 400/100 mg orally twice daily for 10 days. Comparing to the Lopinavir/Ritonavir group, the percentages of patients who became SARS-CoV-2 negative in the CQ group were slightly higher at day 7, day 10, and day 14. By day 14, the incidence rate of lung improvement based on CT imaging from the CQ group was more than doubled to that of the Lopinavir/Ritonavir group (rate ratio 2.21, 95% CI 0.81-6.62). By day 14, all 10 patients (100%) from the CQ group were discharged compared to 6 patients (50%) from the Lopinavir/Ritonavir group. These results demonstrated that CQ is superior to Lopinavir/Ritonavir in promoting a virus negative conversion, inhibiting the exacerbation of
pneumonia, improving lung imaging findings, and shortening the duration of hospital stays. It suggests that CQ may be an effective and inexpensive drug to fight COVID-19.

**Safety Issues**

As an old drug used in clinical practice for decades, both CQ and HCQ show high tolerance even during pregnancy. For a long time, CQ has been controversial for its narrow therapeutic window concentration to the toxic concentration, while HCQ, which is similar to CQ in a therapeutic effect, has been more favored for its less toxicity. Still, the toxicity of CQ or HCQ is considered to be dose-related and the probability of severe adverse effects at a therapeutic dose is rather low. Therefore, it is critical to maintain a stable blood concentration during administering CQ, not only given to exert its antiviral effect but also in order to avoid the toxicity by excessive accumulation in circulation.

According to Akpovwa, we found that CQ did exert a significant antiviral effect in vitro experiments but the results from animal models and clinical trials were not satisfactory. Hence some scholars speculated that the CQ dosage was insufficient to reach the steady blood concentration, which we now understand is necessary for the treatment of diseases caused by acidic pH-dependent virus. Some in vitro studies have shown that CQ at a range of 10-20 μM/L in blood might be optimal for cell uptake, while a lesser uptake might occur at a concentration above 30 μM/L because higher concentrations of chloroquine existed in the form of the free base. In vivo, the toxicity threshold was found to be of 17.7 μM/L. A concentration of 16 μM/L in whole blood is considered the steady state, and is sufficient to alkalize acidic organelles and inhibit viral replication and excessive release of cytokines, without significant cardiovascular events. From the above studies, it can be concluded that the steady-state CQ concentration in the whole blood of 16 μM/L may be an effective and safe concentration for antiviral treatment. Nevertheless, due to the individual differences in the pharmacokinetics of CQ, the dosage to maintain the above effective concentration still needs to be further studied.

**Adverse Effects**

The adverse effects of CQ in short-term treatment are rare and reversible. Common adverse effects, include headache, dizziness, tinnitus, gastrointestinal reaction, irritability, and skin itchiness. During long-term treatment, such as in the treatment of rheumatic diseases, the most apparent side effect is visual impairment. Large dosage or rapid intravenous administration can lead to hypotension, cardiac dysfunction, abnormal electrocardiogram, cardiac arrest; while single dosage higher than 5 g can be an accurate predictor of a fatal outcome. The other occasional adverse effects, include hypoglycemia, myopathy, hemolysis, acute liver injury, hair loss, gray hair, etc.

**Acute toxicity**

Riou et al. reported that the lethal dose of CQ in a single dose of acute toxicity was 3-5 g, and therefore this dosage was chosen as the criterion for severe CQ poisoning. Nevertheless, it may be more accurate to determine the dose of CQ ingested per kilogram of body weight. The National Institutes of Health webpage reported that the lowest toxic dose for acute CQ poisoning in adults was 138 mg/kg body weight, and the lowest lethal dose was 179 mg/kg body weight (Table I). However, the blood concentration may be of higher value in the determination of acute CQ poisoning due to the interindividual differences in the pharmacokinetics of CQ absorption.

Acute CQ poisoning can be manifested as follows: nausea, vomiting, alalia, visual impairment, dyspnea due to pulmonary edema, and apnea, cardiac arrhythmia, seizures, coma, and even death. For patients with severe CQ poisoning, the criteria for predicting fatal risk include single ingested dose ≥5 g, a systolic pressure ≤80 mm Hg, and QRS duration ≥0.120 s on an electrocardiogram, some presented hypokalemia in severe cases. Severe CQ poisoning is usually fatal. The cardiovascular toxicity of CQ is related to the transiently high blood concentration present early in the distribution phase and toxic effects usually do not persist for more than 24 h after CQ ingestion. Marks indicated that early mechanical ventilation combined with diazepam and epinephrine might be effective in the treatment of severe CQ poisoning.

**Cumulative Toxicity**

The most common side effect of long-term use of CQ is visual impairment. CQ has a strong binding affinity to with melanin cells in the body, which makes it easier to deposit on the cornea and retina, resulting in corneal diseases and retinopathy. Following termination of treatment, corneal changes are usually entirely reversible. However, the changes in the retina, for instance retinitis pigmentosa, vision loss, optic atrophy, visual field defects, and blindness are irreversible.
An accumulative dosage above 100 g increases the risk of retinopathy. Retinopathy can also occur even at doses not exceeding 250 mg per day\(^6\). The American Academy of Ophthalmology (AAO) summarized the risk factors assumed to play key roles in the development of retinopathy as (1) high daily dosage per kilogram body weight (>6.5 mg/ kg of HCQ or >3 mg/ kg of CQ); (2) long duration of consistent intake (>5 years); (3) high body fat level (High body fat level was defined as a BMI >25 kg/m\(^2\)); (4) inherent liver or kidney disease; (5) concomitant retinal disease; (6) age >60 years. It is also suggested that patients should have regular ophthalmologic screening, of which intervals should be based on the risk profile\(^6\).

### Table I. Acute effects of chloroquine phosphate as reported in NIH webpage.

<table>
<thead>
<tr>
<th>No.</th>
<th>Gender</th>
<th>Test Type</th>
<th>Route of administration</th>
<th>Dosage</th>
<th>Adverse effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Woman</td>
<td>TDLo</td>
<td>oral</td>
<td>600 mg/kg/17W</td>
<td>Peripheral nerve and sensation: spastic paralysis with or without sensory change; sense organs and special senses: other: eye; behavioral: changes in motor activity (specific assay)</td>
<td>Marks JS. Motor polyneuropathy and nystagmus associated with chloroquine phosphate. Postgrad Med J 1979; 55: 569.</td>
</tr>
<tr>
<td>4</td>
<td>Man</td>
<td>TDLo</td>
<td>oral</td>
<td>8.571 mg/kg</td>
<td>Gastrointestinal: nausea or vomiting; gastrointestinal: other changes</td>
<td>Bhasin DK, Chhina RS. Chloroquine phosphate induced haematemesis. Hum Toxicol 1989; 8: 387-388.</td>
</tr>
<tr>
<td>5</td>
<td>Man</td>
<td>TDLo</td>
<td>oral</td>
<td>8.571 mg/kg</td>
<td>Gastrointestinal: ulceration or bleeding from duodenum; gastrointestinal: nausea or vomiting; gastrointestinal: other changes</td>
<td>Bhasin DK, Chhina RS. Chloroquine phosphate induced haematemesis. Hum Toxicol 1989; 8: 387-388.</td>
</tr>
<tr>
<td>8</td>
<td>Man</td>
<td>LDLo</td>
<td>oral</td>
<td>179 mg/kg</td>
<td>Null</td>
<td>Ifftsits-Simon C. Fatal, suicidal chloroquine poisonings. Arch Toxikol 1968; 23: 204-208.</td>
</tr>
</tbody>
</table>

It is worth noting that chronic CQ poisoning can also cause cardiomyopathy and skeletal myopathy. In animal models, chronic CQ poisoning can lead to vacuolation and necrosis of cardiomyocytes and skeletal muscle cells, with more severe myocardial injury. They are generally more severe in the region of the ventricular septum than in the rest of the ventricles. Ladipo et al. reported a complete cardiac conduction block caused by chronic CQ poisoning, in which the blood concentration of CQ was more than twice higher than that in the other patients receiving therapeutic doses of CQ; and the ratio of CQ to its metabolites in the heart block patients was significantly lower than that in the other patients receiving therapeutic doses of CQ.

Conclusions

Although the antiviral mechanism of CQ is not fully understood, a large number of studies have shown the antiviral effect of CQ, a potential candidate in emergency viral contagions. Because of the narrow therapeutic window of CQ, it is of utmost challenge for us to formulate an appropriate treatment scheme, which can not only achieve effective antiviral concentration but also avoid the occurrence of severe adverse reactions.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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