



Medical Intelligence Report

Date: March 20, 2020

Topic: Chloroquine for COVID-19
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Chloroquine or Hydroxychloroquine

Chloroquine and hydroxychloroquine are derivatives of quinine, the malaria treatment, that have also been found to have inhibitory effects on RNA viruses (Devaux et al., 2020). Hydroxychloroquine was developed as an alternative to chloroquine to reduce the toxic effects that develop at the high dosage levels.

Quinine derivatives have been found to be useful in the treatment of a range of other illness in addition to malaria, such as auto-immune disorders as well as bacterial, fungal, and viral infection. There have also been studies of the effect of quinine derivatives on HIV infection, which indicated that the medications could inhibit the viral replication cycle in cell culture, but the effect was not robust enough for use as a treatment. There are multiple laboratory experiments of anti-viral activity on a wide array of RNA viruses, but these effects have not always been evident later in patients enrolled in clinical trials. The effects of treatment seem to be very dependent on the concentration of chloroquine used, the duration of treatment, and the clinical team in charge of the trial.

Quinine derivatives are thought to act against viruses by reducing the acidity at the point where the virus is entering the cell, thus preventing infection (Wang, 2020). This action of increasing the pH of a compartment in the cell called the endosome, keeps the viruses outer shell from fusing with the cell and releasing the contents. Later in viral production, the changes in the endosome also interfere with the correct modification of the spike proteins, which prevents them from interacting with cellular receptors on new, human cells.

The immune-modulating effect of quinine derivatives is also thought to contribute to their anti-viral effects.

Effectiveness of Quinine Derivatives on SARS and MERS

During the outbreaks of SARS (2003) and MERS (2012), quinine derivatives were utilized as an experimental treatment. There was evidence of therapeutic effect with chloroquine in people with SARS-Cov, but the effect was less reproducible in people with MERS.

Cell Culture Investigations

Cell culture experiments of the effect of chloroquine on SARS-CoV-2 infection indicate that the drug does disrupt the viral life-cycle at both the entry to cells and later during virus manufacture. The effect of chloroquine on cells occurred at a low concentration of the drug that the authors felt was achievable using the typical oral dosing and at levels normally considered as safe (Wang, 2020).

Another published report compared the effect of chloroquine with hydroxychloroquine. Cell culture experiments showed that hydroxychloroquine was more potent at inhibiting SARS-CoV-2 than chloroquine (Yao et al., 2020).

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Efficacy in Individuals with COVID-19

A published report of the use of chloroquine in Hunan Province showed promising effects in 100 people with COVID-19 (Gao, 2020 and Devaux et al., 2020). The researchers observed a more rapid decline in fever and improvement of lung CT scans, and individuals treated with chloroquine required a shorter time to recover compared with control groups. Importantly, severe adverse reactions were not noted.

The details of this study are sparse, and it was not registered in the clinical trial registries either in China or the world-wide database administered by the National Institutes of Health in the United States (ClinicalTrials.gov). Because of the lack of information on dosing, length of treatment, methods to measure recovery, etc., it is difficult to ascertain the validity of the claims in the report.

Another important unknown is the severity of the illness of those treated with chloroquine in the report from China. There is some preliminary evidence that different treatments for COVID-19 may be more effective when given early in disease progression to prevent severe symptoms, but there is a reduced effect of the drug in people who already have severe symptoms.

Further study is ongoing, and a search of ClinicalTrials.gov indicated five trials with chloroquine for treatment of COVID -19 and four with hydroxychloroquine. Authors of a review of chloroquine or hydroxychloroquine with COVID-19 reported that there are 23 ongoing trials listed on the Chinese registry of clinical trials.

Side Effects of Chloroquine

The use of chloroquine is associated with several safety challenges. At the levels and dosing period needed for treatment of malaria, there is evidence of toxicity. The levels required for treatment of COVID-19 are obviously still being evaluated.

There is evidence that some of the negative effects of chloroquine are cumulative, which means that the longer people take the drug the more likely they are to develop adverse reactions (Devaux, 2020). Also, both chloroquine and hydroxychloroquine have a long half-life in the body (around 50 days), which means that the effects of using the drug will be present for a long time after treatment is stopped. They are also widely distributed in the body, meaning that many different tissues will be exposed during treatment (Schrezenmeier, 2020). In studies using hydroxychloroquine in the treatment of rheumatoid arthritis, it has also been found that the amount of the drug available in the blood varies between patients on the same dose, and even in the same patient at different time points. The basis of this difference is not known. Use of chloroquine has also been found to change the blood levels of other drugs. A study of digitoxin (used for heart failure and irregular heartbeat) showed that use of digitoxin with chloroquine led to a fourfold increase in the amount of digitoxin in the blood. It is thought that chloroquine interrupts one of the common metabolic pathways used by the body to process drugs and remove them from circulation (cytochrome P450).

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**Adverse reactions previously reported with use of chloroquine:**

- Macular retinopathy, retinal damage
- Cardiomyopathy
- Cardiac rhythm disorders
- Gastrointestinal effects, including nausea, vomiting, diarrhea and abdominal discomfort
- Headache
- Skin rash or itching
- Hair loss
- Mood or mental changes

(MedlinePlus, 2020)

Retinopathy is more commonly associated with chloroquine than with hydroxychloroquine, however new studies suggest that hydroxychloroquine-related retinopathy is more common than previously realized (Schrezenmeier, 2020). Because both drugs are cleared from the body through the kidneys, individuals with kidney disease or reduced kidney function are more likely to develop retinopathy.

In recommendations for the use of chloroquine for the treatment of COVID-19, a number of precautions have been recommended to monitor possible adverse effects of the drug. The Chinese recommendations suggest regular blood tests to monitor development of anemia, thrombocytopenia or leukopenia (reduction in red and white blood cells), disturbances in the serum electrolyte levels, and dysfunction in the liver or kidneys. It was also suggested that people being treated with chloroquine receive routine electrocardiography to monitor changes in heart rhythm. Patient interviews are also done on a regular basis to identify visual and mental disturbance or deterioration. The Dutch Center of Disease control stresses the need for stopping treatment at day 5 to reduce the risk of side effects, considering the long half-life of the drug, and the need to differentiate between chloroquine phosphate and chloroquine base because the doses are different.

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