The Benefits of Antiviral Use of Chloroquine Versus its Potential Cardiovascular Side Effects

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During the ongoing COVID-19 pandemic, chloroquine and hydroxychloroquine, which are broadly used antimalarial drugs, have rapidly gained worldwide attention for their possible ability to control the causative virus. However, the clinical impact of these drugs against the virus in humans has not been determined.

Hydroxychloroquine has been used as an antimalarial. Recently, it is also used to treat autoimmune diseases such as lupus and rheumatoid arthritis. In Japan, the drug was officially approved for lupus in 2015. We should take into consideration the risks associated with chloroquine and hydroxychloroquine toxicity, which can cause life-threatening cardiovascular disorders, including myocardial toxicity, QTc interval prolongation, and cardiac arrhythmias, as reported by Kang, et al., because the therapeutic margin seems to be narrow.1 It is also known that the risk of adverse outcomes of the therapy is higher among the elderly, which is a population more likely to have comorbidities and/or be taking medications that cause QTc prolongation. Thus, chloroquine and hydroxychloroquine use should be carefully considered. Also, the dose should be decided according to the patient’s comorbidities and condition.

The problem is that the recommended doses for the treatment of COVID-19 are higher than conventional chronic low-dose therapy, at least during a specific period. Thus, especially for high-risk populations with significant comorbidity burdens, it may be prudent to obtain a routine electrocardiogram before initiating these drugs. While being careful about azithromycin, which is also known to prolong the QTc interval, it would be better to avoid a combination regimen that includes chloroquine in patients with prolonged QTc.

The in vitro antiviral activity of these drugs has been known since the late 1960s. The positive effect against many different viruses, including the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), also known as the SARS coronavirus, has also been reported in animal models. However, chloroquine did not prevent influenza infection in a randomized, double-blind, placebo-controlled clinical trial,3 and did not affect dengue-infected patients in a randomized controlled trial.4 Moreover, the clinical trial, conducted during the chikungunya fever outbreak in 2006 in Réunion Island, showed that oral chloroquine treatment did not improve the clinical consequences.5 Given the results of previous reports, no acute virus infection has been successfully treated by these drugs in humans.

Some possible mechanisms for the antiviral activity or anti-inflammatory effects of these drugs have been reported. For example, their weak alkalinity increases endosomal pH in host intracellular organelles.6 The pH increase inhibits autophagosome-lysosome fusion and inactivating enzymes that viruses require for replication.7 Another group suggested that chloroquine can interfere with the glycosylation of angiotensin-converting enzyme-2 (ACE II), the receptor that SARS-CoV-2 uses to enter cells.8 Also, a series of immunomodulatory and anti-inflammatory effects via inhibition of toll-like receptor stimulation and nuclear factor kappa light-chain-enhancer of activated B cell pathways in macrophages is supposed to reduce processing of the ligands for antigen presentation to T cells. This immunomodulation of chloroquine may be an essential mechanism for the clinical consequences during infection.9,10

An expert consensus about the use of chloroquine was published on February 20, 2020 by a multicenter collaboration group of the Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province, China. However, not much information was provided on the method used to achieve consensus. Currently, at least 80 trials of chloroquine and/or hydroxychloroquine, in combination with other drugs in some trials, have been registered worldwide.

In the absence of well-evaluated data at this point in
time, it is difficult to conclude there is sufficient rationale and evidence for using these drugs to treat patients with the virus. The indication of chloroquine or hydroxychloroquine against COVID-19 should be carefully considered in light of the potential detrimental effects of the drugs observed in previous attempts to treat acute viral diseases (Figure). To confirm the efficacy of the proposed treatment in prospective trials and to guide future clinical practice, we need more results from well-designed clinical trials.

Disclosure

Conflicts of interest: The authors declare that they do not have any conflicts of interest related to this study.

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