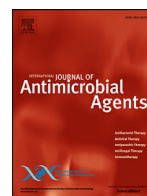




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Aminoquinolines against coronavirus disease 2019 (COVID-19): chloroquine or hydroxychloroquine

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to spread rapidly across China. As of 7 March 2020, the infection was reported from 97 countries globally. To date, 103 882 patients have been confirmed to have COVID-19, of whom 3522 have died [1]. Recently, many trials have been designed to determine an effective therapeutic regimen for COVID-19. Of the target regimens, chloroquine therapy is being considered [2]. Several clinical trials in China have shown chloroquine phosphate, an aminoquinoline used in malaria treatment, to be effective against COVID-19 at a dose of 500 mg/day [3]. Chloroquine phosphate also played a promising role in the management of the Zika virus and SARS-CoV outbreaks. Chloroquine acts by increasing the pH of intracellular vacuoles and altering protein degradation pathways through acidic hydrolases in the lysosomes, macromolecule synthesis in the endosomes, and post-translational protein modification in the Golgi apparatus. In macrophages and other antigen-presenting cells, chloroquine interferes with antigen processing, thereby achieving an antirheumatic response [4]. Studies have demonstrated that chloroquine also confers its considerable broad-spectrum antiviral

effects via interfering with the fusion process of these viruses by decreasing the pH. In addition, chloroquine alters the glycosylation of the cellular receptors of coronaviruses [5]. Hydroxychloroquine (Fig. 1), a less toxic aminoquinoline, has an *N*-hydroxyethyl side chain in place of the *N*-diethyl group of chloroquine. This modification makes hydroxychloroquine more soluble than chloroquine. Similar to chloroquine, hydroxychloroquine increases the pH and confers antiviral effects. In addition, hydroxychloroquine has a modulating effect on activated immune cells, downregulates the expression of Toll-like receptors (TLRs) and TLR-mediated signal transduction, and decreases the production of interleukin-6 [6]. Although the antimalarial activity of hydroxychloroquine is equivalent to that of chloroquine, hydroxychloroquine is preferred over chloroquine owing to its lower ocular toxicity [7]. Retinopathy is a dose-limiting adverse effect of hydroxychloroquine, and a safe daily dose appears to correspond to 6.5 mg/kg of ideal body weight and 5.0 mg/kg of actual body weight [8]. Although there are more clinical data on the anti-coronaviral activity of chloroquine than that of hydroxychloroquine, both of these agents are theoretically similar in their antiviral activity [9]. Moreover, chloroquine is not as widely available as hydroxychloroquine in some countries. In addition, chloroquine is associated with greater adverse effects than hydroxychloroquine. For example, in patients with COVID-19, chloroquine can interact with lopinavir/ritonavir, resulting in prolongation of the QT interval. Hence, it is necessary to consider hydroxychloroquine instead of chloroquine when the latter is not available for treating patients with COVID-19. For

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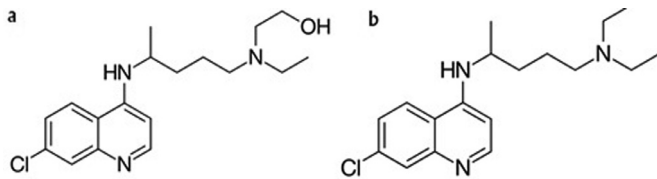


Fig. 1. Chemical structure of (a) hydroxychloroquine and (b) chloroquine.

example, in Iran, there is a serious shortage of chloroquine and hydroxychloroquine can be recommended instead. Other therapeutic agents for COVID-19, such as antiviral agents (oseltamivir, lopinavir/ritonavir, ribavirin, etc.), interferons and intravenous immunoglobulins that do not interfere with hydroxychloroquine, are currently under investigation.

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