Canadian Society of
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COVID-19, Chloroquine and Hydroxychloroquine: Is There Fire Beneath the Smoke?

A Position Statement Endorsed by the Canadian Society of Pharmacology and Therapeutics

The current COVID-19 pandemic has worldwide impacts including a large number of infections, many deaths and economic and social hardship. There currently is no vaccine for COVID-19 and no established therapy beyond excellent supportive care.

In the absence of experimental evidence for efficacy and safety of specific therapies for COVID-19, a number of treatments have been suggested. One approach that has attracted attention in mainstream and social media has been the use of chloroquine or hydroxychloroquine. These drugs originally developed for the prophylaxis and treatment of malaria are aminoquinolones that have also been used for the therapy of autoimmune disease such as lupus and rheumatoid arthritis. There has been considerable interest in the use of aminoquinolones for the therapy of COVID-19 due to the lack of a known effective specific therapy, the lack of a vaccine and the rapid and aggressive spread of the virus.

The pharmacological basis for the use of chloroquine and hydroxycholoquine for COVID-19 dates back to the 1960s, when *in vitro* studies demonstrated that chloroquine had a wide range of antiviral effects. In the case of the SARS-CoV-2 , the virus causing the COVID-19 pandemic, this may be due to interference with cell-viral fusion or glycosylation of viral cell receptors (1,2). As well, immunomodulatory effects of chloroquine and hydroxychloroquine may inhibit the evolution of the serious complications of COVID-19 infection such as cytokine storm.

Initial reports from small observational studies suggested that therapy with chloroquine or hydroxychloroquine may have been associated with reduced exacerbations of pneumonia and more rapid viral clearance (3,4). The results of these initial studies have generated considerable interest for the therapeutic potential of chloroquine and hydroxycholoquine for COVID-19. However aminoquinolone therapy is known to be associated with a risk for significant adverse drug reactions.

Both chloroquine and hydroxychloroquine are associated with the risk for serious adverse drug reactions, including retinal toxicity, myopathy and drug-induced QTc prolongation which can lead to fatal arrhythmias (5,6). Adverse drug reaction risk is believed to be somewhat lower with hydroxychloroquine than chloroquine. As well, there have been fatalities associated with the use of non-pharmacologic aminoquinolones such as fish tank cleaners in the context of the COVID-19 pandemic.

Four recently completed studies have provided insights on the potential role – or lack thereof – of aminoquinolones in the therapy of COVID-19. A double-blind randomized Brazilian study of 81 patients comparing different dosage regimens of chloroquine comparing a 450 mg once daily dose to a 600 mg twice daily dose found a significant increase in serious adverse events in the high dose arm, mandating early termination of the high dose arm and conversion of all patients to the low dose arm (7).

An open-label randomized study of 150 patients in China comparing standard care to standard care plus hydroxychloroquine with a loading dose of 1200 mg for 3 days followed by 800 mg daily demonstrated no difference in the 28 day negative conversion rate for COVID-19 between the two groups (8). There was no difference symptom alleviation overall although there was a difference seen in favour of the hydroxychloroquine group when the confounding effects of anti-viral drugs were corrected for in a post-hoc analysis. There was a statistically significant reduction in inflammatory markers such as C-Reactive Protein in the hydroxychloroquine treated group. There were more adverse effects seen in the hydroxychloroquine treated group (30%) versus the standard of care group (9%) with two serious adverse events in the hydroxychloroquine treated group.

A French study analyzing data on 181 patients from 4 hospitals compared the outcomes in 84 patients treated with hydroxychloroquine versus 97 who were not treated. The results demonstrated no significant difference in outcomes although eight patients in the hydroxychloroquine group had electrocardiogram abnormalities that mandated cessation of aminoquinolone therapy (9).

An American retrospective analysis of 368 military veterans treated with supportive care only, hydroxychloroquine or hydroxychloroquine plus azithromycin found no evidence of benefit from hydroxychoroquine monotherapy and an increased risk of overall mortality (10).

Based in part on these findings and the known safety risks associated with QTc prolongation the FDA has recommended that chloroquine and hydroxychloroquine should not be used to treat COVID-19 except in a hospital setting or in a clinical trial (11). The FDA emphasized that this did not apply to FDA approved uses for chloroquine and hydroxychloroquine that are for malaria, lupus and rheumatoid arthritis. Health Canada has also issued a warning to the public and physicians as to the use of chloroquine and hydroxychloroquine for the treatment of COVID-19 and cautioned that this should only be in the context of a clinical trial (12).

In summary while there is interesting *in vitro* data suggesting a potential role for chloroquine or hydroxychloroquine in the therapy of COVID-19, the very real potential for toxicity and lack of evidence of efficacy in the best practice trials conducted to date suggest that chloroquine or hydroxychloroquine for COVID-19 should only be used in the context of a controlled and well designed clinical trial or after the thoughtful consideration of an infectious disease consultant.

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