REVIEW

Safety considerations with chloroquine, hydroxychloroquine and azithromycin in the management of SARS-CoV-2 infection

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly around the globe in recent months. With deaths from its associated disease, coronavirus disease 2019 (COVID-19), projected to reach into the millions and a vaccine unlikely in the near term, the search is on for existing drugs that might prevent COVID-19 or improve outcomes for patients who have COVID-19. Chloroquine and its derivative hydroxychloroquine, which have been used for decades in the treatment and prevention of malaria as well as chronic inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus, have received much attention as potential therapies.

Optimism for repurposing these drugs stems from 2 lines of evidence: inhibition of *Coronaviridae* (including SARS and SARS-CoV-2) in vitro[1–3] and preliminary but contradictory clinical data from studies conducted in China and France.[4–8] Of these, an open-label nonrandomized study by Gautret and colleagues[5] that involved treatment using hydroxychloroquine (combined in some patients with azithromycin, an azalide antibiotic with putative antiviral properties[9]) has garnered an unusual degree of attention. Despite this study's small sample size and serious methodologic limitations, on Mar. 21, 2020, President Donald Trump touted the drug combination as having "… a real chance of being one of the biggest game-changers in the history of medicine."[10] Within days of this pronouncement, chloroquine-related deaths were reported in Africa and Arizona (www.theguardian.com/world/2020/mar/24/coronavirus-cure-kills-man-after-trump-touts-chloroquine-phosphate; www.cnn.com/2020/03/23/africa/chloroquine-trump-nigeria-intl/index.html).

As we await further evidence on the role, if any, of these drugs in addressing the SARS-CoV-2 pandemic, many clinicians have already begun using them to treat COVID-19. The most typical regimen is 5 days of hydroxychloroquine at daily doses of 400–600 mg, which delivers a cumulative dose comparable to what might be given over 48 hours for chloroquine-sensitive malaria caused by *Plasmodium falciparum*. The US Food and Drug Administration has granted emergency authorization for

the use of chloroquine and hydroxychloroquine for treatment of COVID-19,[11] and the Indian Council of Medical Research COVID-19 National Task Force has advocated extended hydroxychloroquine prophylaxis for health care workers.[12]

This review provides a general overview of potential harms associated with use of chloroquine and hydroxychloroquine — and to a lesser extent azithromycin — and a discussion of the management of adverse events, based on best available evidence (Box 1).

KEY POINTS

- Chloroquine and hydroxychloroquine are generally well tolerated, but clinicians and patients should be aware of serious adverse events that can occur, even during short courses of treatment.
- Potential risks of treatment include prolongation of the QTc interval (especially in patients with preexisting cardiac disease or if coprescribed with azithromycin), hypoglycemia, neuropsychiatric effects, drug–drug interactions and idiosyncratic hypersensitivity reactions.
- Genetic variability in metabolism of these drugs is considerable and influences their safety and effectiveness.
- Chloroquine and hydroxychloroquine are extremely toxic in overdose.
- As we await stronger evidence on the role, if any, of these drugs in the treatment or prevention of coronavirus disease 2019, uncommon but serious harms of treatment can be mitigated by careful patient selection and monitoring.

Box 1: Evidence used in this review

A search of PubMed from 1966 until 2020 was conducted for publications related to adverse events involving chloroquine, hydroxychloroquine and azithromycin. No restrictions were placed on article type; however, reviews were prioritized where available and their bibliographies were examined for articles that might have been missed in the broader search.

What are the potential adverse effects of chloroquine or hydroxychloroquine and azithromycin?

Along with common adverse effects such as pruritus, nausea and headache, chloroquine and hydroxychloroquine can predispose patients to life-threatening arrhythmias, an effect that may be enhanced by concomitant use of azithromycin. Other uncommon but serious potential harms include hypoglycemia, neuropsychiatric effects, idiosyncratic hypersensitivity reactions and drug–drug interactions, with genetic variability playing an important role in each of these. Chloroquine and hydroxychloroquine are also extremely toxic in overdose.

Prolongation of the QTc interval

Both chloroquine and hydroxychloroquine interfere with ventricular repolarization, leading to prolongation of the QTc interval and an increased risk of torsades de pointes (TdP). This effect is dependent on dose: studies involving volunteers found mean increases in QTc of 6.1 ms after a dose of 600 mg and 28 ms after a dose of 1200 mg.[13,14] However, the effect varies among individuals and can be pronounced. Among 30 children given short courses of chloroquine for malaria, 1 experienced an increase in the QTc interval of 64 ms after just 1 day of treatment.[15]

Azithromycin itself does not usually cause clinically significant prolongation of the QTc interval,[16] but its use in combination with either chloroquine or hydroxychloroquine could theoretically increase the risk of TdP. Reassuringly, an animal model found no evidence of such an interaction,[17] and the combination has been used safely in patients with malaria.[18,19] Nevertheless, given limited experience in patients with COVID-19 and the potential for use of these drugs in patients with cardiac disease or those taking other drugs that delay repolarization, monitoring of the QTc interval at baseline and daily for the duration of treatment is advised, especially if azithromycin is coprescribed. Daily monitoring is impractical during prophylactic treatment, but assessment of the QTc interval at baseline is advised, especially for individuals with cardiac disease. It is prudent to correct electrolyte disorders and, where possible, avoid or minimize use of other drugs known to prolong the QT interval (Box 2).

Hypoglycemia

Case reports have described severe hypoglycemia with both chloroquine and hydroxychloroquine in patients with malaria as well as those with lupus and other chronic diseases.[20–23] The basis of this effect (aside from malaria-related hypoglycemia) is multifactorial and includes reduced insulin clearance, increased insulin

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Box 2: Useful resources for clinicians

- The Department of Medicine at the University of Indiana supports a resource to help clinicians anticipate potentially harmful drug interactions (https://drug-interactions.medicine.iu.edu/MainTable.aspx).

- The Credible Meds website (www.crediblemeds.org/) is a resource to help physicians identify other drugs that may prolong the QT interval.

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sensitivity and enhanced pancreatic insulin release.[24] Among 250 patients with poorly controlled type 2 diabetes who were unwilling to start insulin, hydroxychloroquine (400 mg/d) was associated with marked reductions in fasting plasma glucose, hemoglobin A_{1c} and body weight, whereas hypoglycemia developed in 2% of participants over the 48-month study period.[25]

Physicians should warn patients who are being treated with chloroquine or hydroxychloroquine about the possibility of hypoglycemia and describe its manifestations. Management of hypoglycemia involves cessation of the drug and administration of supplemental glucose or parenteral dextrose as needed. For patients with severe or recurrent hypoglycemia, octreotide (50–100 μg administered intravenously or subcutaneously every 8 h) is a well-tolerated somatostatin analogue that inhibits pancreatic insulin release and may be helpful in mitigating the rebound hyperinsulinemia than can ensue after large doses of intravenous dextrose.[26]

Neuropsychiatric effects

Chloroquine and hydroxychloroquine are known to cause a wide spectrum of neuropsychiatric manifestations, including agitation, insomnia, confusion, mania, hallucinations, paranoia, depression, catatonia, psychosis and suicidal ideation.[27] These can occur at all ages,[28] during acute or chronic use,[29–32] and in patients with and without a history of mental illness.[28,32] Resolution is expected upon stopping the drug, although symptoms may not resolve quickly.[33] Patients and clinicians should recognize new or worsening neuropsychiatric symptoms as possible adverse effects of treatment. Indeed, given the speculative nature at present of antimalarial agents in the prevention or treatment of SARS-CoV-2 infection, an argument can be made for avoiding these drugs in patients with underlying mental illness until more data are available.

Hematologic toxicities

Many clinicians associate antimalarial agents with oxidative hemolysis, particularly in patients with severe variants of glucose-6-phosphate dehydrogenase (G6PD) deficiency. Primaquine is well known to cause this, but chloroquine and hydroxychloroquine are much less likely to do so. In a chart review of 275 rheumatology patients with established G6PD deficiency, no episodes of hydroxychloroquine-related hemolysis were identified over more than 700 months of treatment.[34] Hematologic abnormalities including lymphopenia, eosinophilia and atypical lymphocytosis can be features of immunologically mediated idiosyncratic drug reactions, as discussed below.

Genetic variability

Both chloroquine and hydroxychloroquine are metabolized by hepatic cytochrome P450 enzyme 2D6 (CYP2D6), the expression of which varies among individuals as the result of genetic polymorphisms.[35,36] Roughly 7% of white North Americans have no functional CYP2D6 (the "poor metabolizer" phenotype) and 1%–2% have gene duplications conferring an "ultrarapid metabolizer" phenotype, although the prevalence of these varies based on ethnicity.[37] This genetic variability influences the response to treatment for malaria and chronic inflammatory diseases, as well as the risk of adverse events.[38,39]

Drug–drug interactions

In addition to being substrates for CYP2D6, chloroquine and hydroxychloroquine inhibit its activity, most likely by competitive inhibition.[40] This has the potential to influence the fate of other drugs reliant on CYP2D6 for metabolism. For instance, hydroxychloroquine increases systemic exposure to orally administered metoprolol levels by about 65% and peak concentrations by 72%.[41] Although data are limited, it is reasonable to assume that chloroquine and hydroxychloroquine potentiate other CYP2D6 substrates (including carvedilol and many others), and undermine the effectiveness of prodrugs reliant on CYP2D6 for activation such as codeine and tramadol.[42] Indeed, the potential exists for chloroquine and hydroxychloroquine to precipitate opioid withdrawal in patients who are taking these drugs regularly.

Unlike the related drugs erythromycin and clarithromycin, azithromycin exhibits little inhibition of cytochrome P450 enzymes or drug-transport proteins such as P-glycoprotein.[43] As such, azithromycin is far less likely to precipitate clinically important drug–drug interactions (Box 2).

Immunologically mediated adverse reactions

Chloroquine and hydroxychloroquine have been implicated in severe cutaneous adverse reactions, including Stevens–Johnson syndrome,[44] toxic epidermal necrolysis,[45,46] DRESS (drug reaction with eosinophilia and systemic symptoms)[47,48] and others. Although rare, these entities should be considered in patients with new-onset fever, exanthem or mucositis in the weeks after the start of treatment, particularly when accompanied by new hematologic abnormalities (such as lymphopenia, eosinophilia or atypical lymphocytosis) or unexplained liver or kidney injury.

Other safety concerns

There is no evidence that chloroquine, hydroxychloroquine or azithromycin are harmful to the developing fetus, and pregnancy is not a contraindication to their use.[49,50] Long-term risks of treatment include retinopathy, vacuolar myopathy, neuropathy, restrictive cardiomyopathy and cardiac conduction disturbances.[51–53] These risks are negligible in the context of treatment of SARS-CoV-2 but may be relevant if they are used for extended prophylaxis.

Overdose

Chloroquine and hydroxychloroquine are extremely toxic in overdose, sharing several manifestations in common with cyclic antidepressant poisoning. Deliberate or inadvertent overdose leads to rapid onset of central nervous system toxicity (seizures and coma), cardiovascular collapse (including inhibition of cardiac sodium and potassium channels resulting in QRS widening and QT interval prolongation, respectively) and hypokalemia resulting from intracellular shifting.[54] Treatment of overdose is largely supportive and includes prompt administration of activated charcoal, intravenous benzodiazepines and vasopressors as needed, sodium bicarbonate or hypertonic saline for substantial QRS widening and related arrhythmias, and judicious management of hypokalemia while taking care to avoid overcorrection. Urgent consultation with a poison control centre is advised in all cases.

Could use of these drugs potentially worsen COVID-19?

Despite optimism (in some, even enthusiasm) for the potential of chloroquine or hydroxychloroquine in the treatment of COVID-19, little consideration has been given to the possibility that the drugs might negatively influence the course of disease. For example, some have speculated that inhibition of T-helper cell proliferation and interleukin-2 production or responsiveness might inadvertently augment the inflammatory response in patients who are infected, negatively influencing patient outcomes.[55] Although somewhat counterintuitive, the possibility that these drugs might adversely influence outcomes underscores the urgent need for high-quality randomized controlled trials in the face of a growing pandemic.[56]

Could use of these drugs to treat or prevent COVID-19 lead to shortages for other patients?

The immunomodulatory effects of hydroxychloroquine are critical to a subset of patients with systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, sarcoidosis and other chronic diseases. A surge in prescriptions based on speculation about their role in the prevention or treatment of SARS-CoV-2 infection threatens the availability of these drugs for patients with chronic inflammatory disorders for whom they are known to be effective. At least 2 manufacturers have announced plans to increase hydroxychloroquine production in anticipation of this need.[56]

Conclusion

The use of either chloroquine or hydroxychloroquine and azithromycin for treatment or prevention of SARS-CoV-2 infection is currently supported primarily by in vitro data and weak studies involving humans. Physicians and patients should be aware of several uncommon but potentially life-threatening adverse effects should these drugs be used before better-designed studies determine their benefit, if any, in treating or preventing COVID-19. Harms of treatment can be mitigated by careful patient selection and monitoring.

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