New American

Written by **Dennis Behreandt** on July 20, 2020

Published in the July 20, 2020 issue of the New American magazine. Vol. 36, No. 14

The Science of Hydroxychloroquine

It is one of the most commonly used drugs in the world. It has been available for decades and millions of people use it every day. Doctors recommend it to treat fevers in children and adults, and they suggest people use it post-surgery. There is good reason for this: It works, and in normal therapeutic doses is reasonably safe. But, like all drugs, there is a dark side to this one.

Because this drug is so readily available and so cheap, most people believe it is among the safest drugs they can take, yet overdoses, even mild ones, can lead to severe health problems. This tendency is exacerbated by the ready availability of extended release formulations that sometimes offer higher-than-normal dosing, making it easier to overdose. As a result, a shocking number of people are killed each year from misuse of this drug.

Writing for *StatPearls*, a peer-reviewed information source for healthcare professionals, researchers Suneil Agrawal and Babak Khazaeni noted that this drug "is the second most common cause of liver transplantation worldwide and the most common in the US. It is responsible for 56,000 emergency department visits, 2600 hospitalizations, and 500 deaths per year in the United States. Fifty percent of these are unintentional overdoses."

Moreover, it seems this drug has unusual psychological impacts on some users. In 2005, researchers from the Ohio State University of Psychology reported that in their study they found that the drug blunted emotions. "Across two studies, we demonstrated that [it] attenuates individuals' evaluations and emotional reactions to negative and positive stimuli alike," they said. The drug, they concluded, should be "described as an all-purpose emotion reliever."

Again, this drug is readily available, among the most used drugs in the world, and is entirely non-controversial. Another drug, although used for different reasons, is similar in some respects. It, too, has been used for decades, and millions of people use it daily. In fact, they need to use it daily or the diseases they suffer from would turn debilitating and deadly. As such, it is widely prescribed for these conditions. And in normal dosing, it is very safe. Still, it can cause cardiac effects that might lead to death, and it can have side effects in the eyes. But a fact sheet from the U.S. Centers for Disease Control (CDC) says that it "can be prescribed to adults and children of all ages. It can also be safely taken by pregnant women and nursing mothers." The CDC fact sheet goes on to say of this drug that it's "a relatively well tolerated medicine."

What are these drugs? The first, the one that sends over 50,000 people to emergency rooms and kills

500 people per year, is acetaminophen, the active ingredient in the painkiller Tylenol. The second, a drug used to treat the deadly disease of malaria along with lupus and rheumatoid arthritis, is none other than prescription hydroxychloroquine (HCQ) — famous of late for its controversial role in fighting the COVID-19 pandemic.

The first drug, which has devastating and often deadly side effects, mainly helps ward off fevers and body aches and can be bought over the counter. The second one, which has side effects arguably on par with the first one and is used to treat deadly and debilitating diseases, has been called too dangerous to use to treat COVID-19, which itself is considered so deadly that much of the country was literally locked down to avoid it. So the question becomes: "Are the attacks on hydroxychloroquine medically or politically motivated?" A look at the science should give us the answer.

Media Frenzy

Having shown promise in treating those fighting COVID-19, hydroxychloroquine even attracted the attention of President Trump, who announced in May that he was taking the drug to ward off the disease. "A couple of weeks ago, I started taking it," he said at a meeting of restaurant executives. At the time, CNN reported that the president had "been taking it every day for a week and a half."

That admission made left-wing news outlets and commentators plumb the depths of "Trump derangement syndrome" (TDS). The far-left tabloid *Raw Story*, which somehow seems to consider tweets from random Twitter users to be news, quoted one such random never-Trumper as saying the president wasn't taking hydroxychloroquine at all but that his doctors were probably slipping him Skittles candies instead. Lest anyone think this is just the delirious ravings of someone entering the lunatic phase of TDS, the notion that Trump was lying about his use of the drug was given the imprimatur of no less than MSNBC commentator Joe Scarborough, who told his viewers, "Let me assure you the president of the United States is not taking hydroxychloroquine." Elaborating further, Scarborough continued: "In all the time that I knew him, I only sat for one meal with him. And before that meal, he had wipes like this high and would just go through the wipes, compulsively, and wipe his hands, sanitize his hands before eating anything. So he is not taking something that his own administration has said will kill you, that his own FDA said will kill you, that the VA said will kill you."

Contra Scarborough, perhaps the president was taking it because he was fairly certain it was safe to take as long as he did so under guidance from his physicians.

The tempest over the president's use of hydroxychloroquine is emblematic of the deepening political divide over healthcare and much more in post-COVID America. Like the wearing of masks and the destruction of fundamental liberties via lockdowns, questions about hydroxychloroquine have become less about whether doctors should continue to treat patients with the drug and more about pitting statist control and intervention against personal choice in general, and in health matters in particular, while attempting to corral and control scientific inquiry via leftist propaganda.

Since the president's admitted use of the drug, liberal partisans of centralized power, especially in matters of healthcare, have done their utmost to paint hydroxychloroquine as ineffective and dangerous. Recently, the FDA revoked its Emergency Use Authorization for the drug, and in the wake of that action, the World Health Organization, claiming that it has shown no benefit in testing, has stopped its investigation of the drug for treatment of COVID-19.

While some studies have indeed found little or no benefit from hydroxychloroquine for fighting SARS-CoV-2, the virus behind the pandemic, other studies — and doctors using the drug to treat patients — have shown the opposite, crediting the drug with saving lives.

Scientifically and clinically, properly understanding the potential of this drug is critical. If it can, in fact, be used to save lives, how it does so, and under what conditions it might work, must be understood. This includes investigation of how and why it might work in combination with other substances, even if, on its own, it has little or no effect. By contrast, propaganda and fearmongering that hamper proper use of the drug and cause an end to scientific inquiry into the drug literally put lives at risk.

And in the present case, as we shall demonstrate, hydroxychloroquine continues to represent an intriguing potential option for the treatment of COVID-19.

In Vitro

The term *in vitro* means "in the glass" and refers to scientific work on biological subjects, including microorganisms, cells, and chemistries, separated from their normal biological context. In in vitro studies, chloroquine (CQ) and hydroxychloroquine have been shown to have antiviral properties, including for SARS-CoV-2.

In a letter to — and published by — the journal *Cell Research* in February, a team of Chinese researchers described the effect of chloroquine on SARS-CoV-2 in vitro. Their study included tests of the antiviral drug Remdesivir, along with chloroquine and several other antiviral drugs.

"Notably," they reported, "two compounds remdesivir and chloroquine potently blocked virus infection." For chloroquine, they went on to note of their findings that their work "demonstrated that chloroquine functioned at both entry, and at post-entry stages of the 2019-nCoV [now renamed SARS-CoV-2] infection." In addition to "its antiviral activity," they continued, "chloroquine has an immune-modulating activity, which may synergistically enhance its antiviral effect in vivo."

The researchers concluded that chloroquine is "highly effective in the control of 2019-nCoV infection in vitro," and they suggested that both it and remdesivir "should be assessed in human patients suffering from the novel coronavirus disease."

Another team of Chinese researchers also justified exploring hydroxychloroquine's impact on SARS-CoV-2, in an article submitted to and published by the journal *Clinical Infectious Diseases*, published by no less than Oxford University Press for the Infectious Diseases Society of America. It, too, cited the research published earlier by *Cell Research* as justification for exploration: Noting that the earlier team's findings were "supported by clinical studies conducted in approximately 100 patients with SARS-CoV-2," they argued that because "hydroxychloroquine is an analog of chloroquine that has fewer concerns about drug-drug interactions," and because "in the previous SARS outbreak, hydroxychloroquine was reported to have anti-SARS-CoV activity in vitro," it seemed possible that it might "be a potential pharmacological agent for the treatment of COVID-19 infection."

This team of researchers found that "both chloroquine and hydroxychloroquine have good antiviral activity. Chloroquine and hydroxychloroquine were found to decrease the viral replication." Meanwhile, they reported that "hydroxychloroquine exhibited a superior in vitro antiviral effect in comparison to chloroquine when the drug was added" before exposure to the virus. So, simply, hydroxychloroquine is better than chloroquine.

Based on their experiments, the researchers concluded that "hydroxychloroquine exhibited better in vitro anti-SARS-CoV-2 activity than chloroquine."

Moreover, they pointed out that "an unpublished clinical trial has demonstrated the therapeutic effect of chloroquine in patients with SARS-CoV-2. On the basis of hydroxychloroquine's superior antiviral and prophylactic activity, as well as its more tolerable safety profile in comparison to chloroquine, we believe that hydroxychloroquine may be a promising drug for the treatment of SARS-CoV-2 infection."

In fact, they even concluded that, if administered early, hydroxychloroquine might inhibit the body's own sometimes disordered and aggressive response to the virus, the "cytokine storm" that has been implicated in some COVID-19 deaths from multi-organ failures. Hydroxychloroquine, they concluded, "may be an ideal drug to treat SARS-CoV-2 infection as it can inhibit the virus via its antiviral effects and help mediate the cytokine storm via its immunomodulatory effects. Based on work conducted in our laboratory, we recommend the concomitant use of low-dose hydroxychloroquine with an anti-inflammatory drug to help mitigate the cytokine storm in critically ill patients with SARS-CoV-2."

Early Results in Patients

However promising or interesting the results of in vitro studies may be, the effectiveness of a potential medicine depends on how it acts in vivo, or "within the living." Especially in the human context, biochemical activity in vivo is extremely complex and still a matter of intense scientific investigation. Thus, the potential effectiveness of a medicine as demonstrated in vitro may prove completely useless, or even harmful, when used with a living patient. This may be especially true in cases of sick patients whose biological chemistries may be disordered due to disease activity.

Much, however, is known about hydroxychloroquine, as it has a decades-long history of medical usage, including as a treatment for malaria and for the autoimmune disorders lupus and rheumatoid arthritis. For COVID-19, the early promising results from in vitro studies in China led to studies testing the drug's effectiveness with actual patients.

Chinese researchers Jianjun Gao of the Qingdao University School of Pharmacy and Zhenxue Tian and Xu Yang with the Department of Pharmacy at Qingdao Municipal Hospital summarized the results of early attempts to treat patients with hydroxychloroquine in China.

Writing in the journal *Bioscience Trends*, they reported that a number of studies had been "quickly conducted in China to test the efficacy and safety of chloroquine or hydroxychloroquine in the treatment of COVID-19 associated pneumonia in more than 10 hospitals in Wuhan, Jingzhou, Guangzhou, Beijing, Shanghai, Chongqing, and Ningbo. Thus far, results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course."

Following the results reported by the Chinese researchers in *Bioscience Trends*, a French research team consisting of 18 scientists, including noted hydroxychloroquine researcher Didier Raoult, whose work has been influential, undertook a small study of COVID-19 patients at The Méditerranée Infection University Hospital Institute in Marseille. Patients not treated with hydroxychloroquine, the team reported, were recruited as controls "in Marseille, Nice, Avignon and Briançon centers, all located in South France." In reporting the results of this study, the research team deemed the outcome to be

significant. “For ethical reasons and because our first results are so significant and evident we decide to share our findings with the medical community, given the urgent need for an effective drug against SARS-CoV-2 in the current pandemic context,” they wrote in introducing the outcome of the study.

“We show here,” they continued, “that hydroxychloroquine is efficient in clearing viral nasopharyngeal carriage of SARS-CoV-2 in COVID-19 patients in only three to six days, in most patients.”

Of note, they also found that the addition of azithromycin, an antibacterial drug, proved helpful during treatment. “Our preliminary results also suggest a synergistic effect of the combination of hydroxychloroquine and azithromycin,” they wrote. “Azithromycin has been shown to be active *in vitro* against Zika and Ebola viruses and to prevent severe respiratory tract infections when administrated to patients suffering viral infection. This finding should be further explored to know whether a combination is more effective especially in severe cases,” they concluded.

Another study, this time observational, of “a cohort of 80 relatively mildly infected inpatients treated with a combination of hydroxychloroquine and azithromycin” by another French group of 29 researchers (again including Dr. Raoult), further supported the use of hydroxychloroquine in treating COVID.

In this study, the median age of patients was 52, and 57.5 percent of them “had at least one chronic condition known to be a risk factor for the severe form of COVID-19 with hypertension, diabetes and chronic respiratory disease being the most frequent.”

In their results, the researchers reported, “The majority (65/80, 81.3%) of patients had favourable outcome and were discharged from our unit at the time of writing.” Three of the patients in the study required treatment in ICU, “of whom two improved.” One 74-year-old patient remained in ICU as of the writing of the paper. Sadly, “one 86-year-old patient who was not transferred to the ICU, died,” the researchers reported.

Discussing their results, the authors concluded: “By administering hydroxychloroquine combined with azithromycin, we were able to observe an improvement in all cases, except in one patient who arrived with an advanced form, who was over the age of 86, and in whom the evolution was irreversible. For all other patients in this cohort of 80 people, the combination of hydroxychloroquine and azithromycin resulted in a clinical improvement that appeared superior when compared to outcomes of other hospitalised patients, as described in the literature.”

In another, larger study published in the May-June issue of the journal *Travel Medicine and Infectious Disease*, another French team of researchers, again including Dr. Raoult, provided a retrospective “report on 1061 SARS-CoV-2 positive tested patients treated for at least three days with hydroxychloroquine and azithromycin.”

For results, the study authors said:

We report the outcomes of 1061 COVID-19 patients treated with an HCQ+AZ combination from the time of diagnosis…. We assessed patients who received at least three days of treatment and eight days of follow-up…. The treatment was associated with a low proportion of patients with worsening of the disease, as only 10 patients (0.9%) were transferred to the intensive care unit and a low proportion of death, as only eight (0.75%) patients died (case fatality rate updated April 18th, 2020). It was also associated with a low frequency of persistent viral shedding. In our experience, the treatment was well

tolerated with only a low proportion of adverse events (2.4%), all of which were mild with three discontinuations of treatment (0.3%).

The authors determined, based on these results, that they "consider reasonable to follow the recommendations made in Asian countries for the control of COVID-19, notably in Korea and China that consist in early testing as many patients as possible and treating them with available drugs where this strategy has produced much better results than in countries where no active policy has been implemented outside containment." Such drugs, they said, included hydroxychloroquine.

FDA Backtracks

The Food and Drug Administration, which had earlier issued an Emergency Use Authorization (EUA) supporting the use of hydroxychloroquine in the United States, reversed that declaration in June, claiming that additional studies found no beneficial impact from the use of hydroxychloroquine.

In a letter discussing the revocation of the EUA for the drug, FDA chief scientist Denise Hinton said the agency no longer found the drug likely to be effective in treating COVID-19.

"We now believe that the suggested dosing regimens for CQ and HCQ as detailed in the Fact Sheets are unlikely to produce an antiviral effect," Hinton said in the letter. "Earlier observations of decreased viral shedding with HCQ or CQ treatment have not been consistently replicated and recent data from a randomized controlled trial assessing probability of negative conversion showed no difference between HCQ and standard of care alone," she continued.

As a result the agency concluded, Hinton wrote, that "it is no longer reasonable to believe that oral formulations of HCQ and CQ may be effective in treating COVID-19, nor is it reasonable to believe that the known and potential benefits of these products outweigh their known and potential risks. Accordingly, FDA revokes the EUA for emergency use of HCQ and CQ to treat COVID-19."

In support of its conclusion, the FDA cited a paper from a Chinese team of researchers that was made available as a medRxiv preprint. This research team, in reporting its results, found no relevant benefit to the use of hydroxychloroquine when compared to non-use of the drug in standard treatment. Still, the authors noted that the study was incomplete, and they added their own caveats to their findings. "Our negative results on the antiviral efficacy of HCQ obtained in this trial are on the contrary to the encouraging *in-vitro* results and the recently reported promising results from a non–randomized trial with 36 COVID-19 patients," they wrote. "It should be noted that participants in our trial had mainly mild to moderate disease with a median 16-day delay of HCQ treatment from symptoms onset. Therefore, the negative results of our trial are only applicable to patients with persistently mild to moderate COVID-19."

Moreover, they made this important admission: "Our trial could not answer the antiviral efficacy of HCQ at the earlier state, e.g., within 48h [48 hours] of illness onset, the golden window for antiviral treatment in influenza."

Also cited by the FDA as a study that called into question the effectiveness of hydroxychloroquine was one by a Chinese research team that examined a small group of patients treated with chloroquine (not the safer hydroxychloroquine) between January 27, 2020 and February 15, 2020. Yet far from finding that the chloroquine was ineffective, this study demonstrated the opposite. It reported that "one patient in the Chloroquine group became SARS-CoV-2 negative after treatment for only 2 days." Moreover, they

reported, "There were then steady increases in the number of patients turning negative, cumulating at Day 13 when all of the Chloroquine-treated patients became negative."

This study actually compared chloroquine's effectiveness against the effectiveness of the antivirals Lopinavir/Ritonavir. The researchers found that "patients treated with Chloroquine were discharged from hospital in a much quicker pace. The first patient discharged from hospital was from the Lopinavir/Ritonavir group at Day 8, and the first discharged from the Chloroquine group was at Day 9. Encouragingly, by Day 14, all 10 patients (100%) from the Chloroquine group were discharged compared to 6 patients (50%) from the Lopinavir/Ritonavir group. Furthermore, Chloroquine also appeared to promote quicker recovery compared to Lopinavir/Ritonavir recommended by health authorities in China."

Additionally, the FDA and others have raised concerns about the safety of chloroquine/hydroxychloroquine. In this case, the research team that reported these results noted that "overall, Chloroquine appears well tolerated among the patients we treated."

Still, study results are conflicting. Another retrospective study cited by the FDA was conducted by a group of researchers with a small sample of COVID-19 patients at Cleveland Clinic Abu Dhabi's Critical Care Institute. This study found hydroxychloroquine to be ineffective. "Despite a reported antiviral activity against SARS-CoV-2, we found that HCQ was associated with a slower viral clearance in COVID-19 patients with mild to moderate disease," the study's authors wrote. They also noted, however, that the drug appeared safe. "HCQ use was well tolerated in our patients; we did not observe any side effects," they said. "This might be attributed to the low dosing regimen used in our study (400mg daily)."

In sum, there are studies that suggest positive outcomes from treatment with hydroxychloroquine, and studies that show little or no benefit. There is also a paucity of studies that follow up on the use of hydroxychloroquine in combination with azithromycin or zinc.

Those who are eager to end use and investigation of hydroxychloroquine are quick to point to studies that fail to support the use of the drug, and they do so to the exclusion of studies that show the drug's potential, either alone or in combination with zinc or other medicines. And because this is the general approach favored by the mainstream media, the impression given to the public is that the drug is dangerous and ineffective and that its use is irresponsible.

Research findings, though, do not necessarily support this narrative. If anything, the promise of the drug as a potential life-saving treatment remains. And the need for further research and understanding in this area of research, and in many other areas related to COVID-19, remains substantial.

Clearly, when it comes to the science of hydroxychloroquine, there is no consensus; however, much mainstream propaganda would like to suggest the opposite. Right now, what is obvious instead is that more work needs to be done in the interest of gaining essential knowledge and saving lives.

New American

Written by **Dennis Behreandt** on July 20, 2020

Published in the July 20, 2020 issue of the New American magazine. Vol. 36, No. 14

Photo: AP Images

This article originally appeared in the July 20, 2020 print edition of The New American.

Written by **Dennis Behreandt** on July 20, 2020
Published in the July 20, 2020 issue of the New American magazine. Vol. 36, No. 14