ONLINE FEATURE | Audiological Management of COVID-19 Survivors Treated with Hydroxychloroquine and Azithromycin

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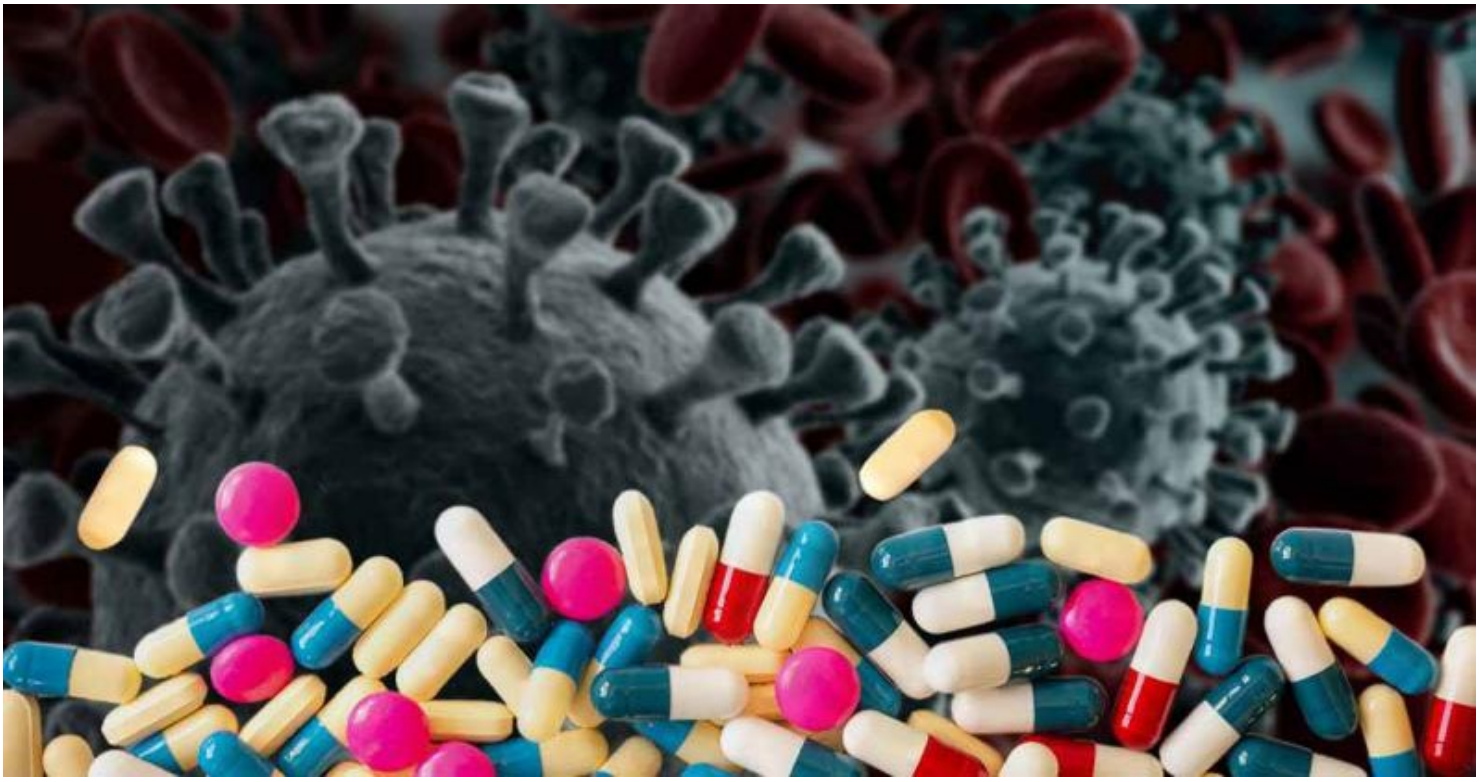
Audiologists have known about the ototoxicity of quinine (and its derivatives) and antibiotics (macrolide and aminoglycoside) for decades. But we have never seen the combined use of two drugs, each with known ototoxic potential, being used as an intervention strategy for the coronavirus pandemic (COVID-19).



In an effort to combat the coronavirus (COVID-19), front-line physicians are re-purposing two drugs: hydroxychloroquine (commonly used for malaria and rheumatoid arthritis) and azithromycin (a macrolide antibiotic used to treat common infections of the respiratory system, the ear and the eye). Both drugs are known ototoxic agents; however, there is no published research about the synergistic ototoxic effects of these drugs in treating COVID-19.

At the present time, it is not known if hearing loss and/or tinnitus will be a late onset side effect of this COVID-19 drug intervention. Therefore, case history questions will need to be added to accommodate this new population of patients.

COVID-19 Infection

The coronavirus disease was identified in 2019 and named/identified as “COVID-19.” The virus is a microscopic parasitic microbe. Once inhaled, the virus will attach itself to the cell’s membrane then duplicate itself destroying more cells in the process. The associated respiratory distress can lead to death.

Medical Intervention

There are no drugs or other therapeutics approved by the U.S. Food and Drug Administration to prevent or treat COVID-19 at the time of this writing. Current clinical management includes infection prevention, control measures, and supportive care, including supplemental oxygen and mechanical ventilatory support when indicated. According to the Centers for Disease Control and Prevention (CDC), interim guidelines for the medical management of COVID-19 will be provided by the Department of Health and Human Services COVID-19 Treatment Guidelines Panel.[1]

Why the Interest in Using Hydroxychloroquine for COVID-19?

The *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2) first broke out in Wuhan, China, in 2019 and subsequently spread worldwide.

Chloroquine, a drug used for malaria, has been sporadically used in treating the SARS-CoV-2 infection. Because hydroxychloroquine shares the same mechanism of action as chloroquine and has a more tolerable safety profile (and more potent than choloroquine), thus making it the preferred drug to treat malaria and autoimmune conditions.[2]

The immunomodulatory effect of hydroxychloroquine also may be useful in controlling the cytokine storm [too many proteins in the blood that causes the immune system to go out of control] that occurs late-phase in critically ill SARS-CoV-2 infected patients. *The authors[2] concluded that there is no evidence to support the use of hydroxychloroquine in SARS-CoV-2.*

Drug Re-Purposing/Off-Label Use

According to the National Institutes of Health’s Center National Center for Advancing Translational Sciences, many drugs approved for other uses already have been tested in humans, so detailed information is available on their pharmacology, formulation and potential toxicity. Therefore, trying an FDA-approved drug for one disease as a new therapy for an unrelated disease could allow the treatment to be ready for clinical trials more quickly, thus speeding Food and Drug Administration review and, if approved, its integration into health care.[3]

FDA approval on a repurposed drug can take approximately three to four years as compared to an investigational new drug (IND), which may take greater than 10 years. The approval rate for a repurposed drug in approximately 30 percent[3] whereas an IND is less than 12 percent.[4]

Emergency Use Authorization

The Emergency Use Authorization (EUA) authority allows the FDA to facilitate the availability and use of medical counter measures (MCM) needed during public health emergencies such as COVID-19.

Under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), unapproved medical products or unapproved uses of approved medical products can be approved in an emergency when there are no adequate, approved or available alternatives.[5]

Currently, there are two drugs that have been proposed for re-purposing for the treatment of COVID-19 patients: **hydroxychloroquine** (Plaquenil® or **chloroquine**) and **azithromycin** (Zithromax® Zithromax Tri-Pak®, Azythromycin Dose Pack®, Zithromax Z-Pak® and Zmax®).

Hydroxychloroquine as a Re-Purposed Drug for COVID-19

Virus versus Cells

According to the American College of Rheumatology, hydroxychloroquine is used to treat rheumatoid arthritis, childhood arthritis, some symptoms of lupus and other autoimmune diseases. “It is believed that hydroxychloroquine interferes with the communication of cells in the immune system.”[6] Essentially the drug blocks the virus from entering the cell and multiplying inside the cell.[7]

Quinine-Related Drugs and Ototoxicity

There are many reports of reversible hearing loss with quinine-related drugs.[8-17]

Claessen, et al.[17] concluded that quinine pharmacokinetics are time-dependent (fast onset of hearing loss): the apparent elimination halftime is shorter in the accumulation phase than in the elimination phase (fast recovery time). The recovery time was longer for the frequencies above 8000 Hz.

Yet other reports indicated that hearing loss from chloroquine was irreversible.[18-22] Hadi, et al.[18] believe that chloroquine aggregates in melanocytes and results in variable injuries to the cochlear sensory hair cells, a decrease in neuronal population, a loss of supporting hair cells and atrophy of stria vascularis. Also, these changes might be caused by an ischemic process.

Mechanism of Action

Quinine like many of the ototoxic drugs preferentially affects high-frequency hearing. In guinea pigs given large doses of quinine, there is degeneration of the Organ of Corti, which begins with loss of the outer hair cells, and may extend to pathological changes in the stria vascularis and inner hair cells.[23]

However, such changes are unlikely to account for the rapid onset and offset of hearing changes as noted in Roche[8]. Vascular alterations, notably vasoconstriction in the stria vascularis, suprastrial ligament and basilar membrane or a direct pharmacological effect on the hair cells may be more relevant to rapid reversible changes in hearing.[24,25]

Ototoxicity is related to the destruction of the stereocilia in varying degrees, reducing the neuron population, altering the support structures, causing atrophy of the stria vascularis and potentially leading to ischemia.[26]

Melanin is present in the inner ear in highly vascular areas; thus, blood vessels are usually surrounded by melanocytes. In this context, it is believed that the buildup of chloroquine is responsible for a vascular injury and degenerative changes in the planum semilunatum and stria vascularis. These abnormalities of the epithelial tissues could result in an alteration of the structure of the endolymph, leading to damage of the cellular receptor. The buildup and long-term retention of antimalarial in melanocytes of the inner ear could explain the late onset of lesions and the relationship with elevated cumulative doses.[27]

The mechanism of hearing impairment may be similar to that associated with salicylism.[8]

Quinine-Related Drugs and Tinnitus

Tinnitus is a common side effect of sensorineural hearing loss; however, the previously cited literature does not report tinnitus with the patients in those studies. Tange[9] noted that tinnitus can occur in small dosages of quinine.

Azithromycin as a Re-Purposed Drug for COVID-19

The clinical efficacy of the combination of hydroxychloroquine and azithromycin was published by French researchers shortly after the *World Health Organization* announced the COVID-19 pandemic on March 12, 2020.[28]

Their findings supported the clinical use of the combination of hydroxychloroquine and azithromycin at the early stage of the COVID-19 infection before the patients develops respiratory distress syndrome with the associated cytokine storm and become less treatable by any antiviral treatment. Despite the small number of patients in the study (22), it gave hope for a “cure” as the disease spread globally.

In the United States, this information led to a media storm about a potential COVID-19 “cure” shortly after a pandemic was declared by the WHO. Because the U.S. Food and Drug Administration has a structured protocol for an investigational new drug (or for drug re-purposing) that requires evidence-based research with a much larger sample of patients than the number in the Gautret study, the information needed a detailed explanation about the FDAs approval process to consumers.

Shortly thereafter the announcement that the hydroxychloroquine and azithromycin combination could be the COVID-19 “cure,” the public became aware that FDA approval of repurposed drugs can take over a year to 18 months following clinical trials.

Please refer to the Emergency Use Authorization section of this article. The Centers for Disease Control and Prevention (CDC) (www.cdc.gov) took the lead in informing the public that a cure for COVID-19 was not going to happen soon (re: FDA clinical trials needed for drug re-purposing). The reader is strongly encouraged to visit the CDC website regularly for the latest news about COVID-19.

Azithromycin Overview

Azithromycin is an antibiotic that is related to erythromycin. Understanding the history of the ototoxicity of erythromycin is important to understand the reason why it has been selected as an adjunct with hydroxychloroquine for the treatment of COVID-19 patients.

Erythromycin was developed in the early 1950s by the Eli Lilly pharmaceutical company. It belongs to the macrolide group of antibiotics.

A macrolide antibiotic inhibits the growth of bacteria and often is prescribed to treat rather common bacterial infections. They are safe, broad spectrum antibiotics with gastrointestinal side effects being the most common.[29] Common uses of this class of antibiotics are for treatment of influenza and other respiratory infections.

The first report of erythromycin-induced ototoxicity did not appear until 1973.[30] The loss was 50 dB at all test frequencies but returned to normal after the drug was discontinued. Similar case reports began to appear in the literature over the next seven years.[31,32]

A comparison of incidence of hearing loss to the erythromycin dosage was examined by Haydon et al.[38] No hearing loss was identified with 22 patients; however, a group of patients emerged as being more susceptible to ototoxicity: those with pre-existing renal or hepatic disease, age (elderly), and gender (female). Demaldent et al.[33] also recommend caution when prescribing erythromycin to patients with renal failure.

Additional case reports of reversible hearing loss after erythromycin had been discontinued have been published.[35,36,37,38] A case-control study published in 1992 reported a relationship between high doses (>2mg/day) of erythromycin and ototoxicity in five of 30 patients. Ototoxicity resolved in all patients within six to 14 days after discontinuation of therapy.[39]

Authors of two studies report that the central auditory pathway may be the site of the impairment.[40,41] However, using auditory brainstem response (ABR) data, Sacristan, et al.[42] showed the absence of waves I to III normalized (all ABR waves) after the drug had been stopped. They concluded that the hearing loss would be peripheral with no involvement of the central pathways.

Another case report[43] showed irreversible hearing loss "with some recovery" after the erythromycin was discontinued. Other case reports identified persistent bilateral sensorineural hearing loss[44] and bilateral residual high-tone sensorineural hearing loss.[45] Vertigo has been reported in a minority of cases.[38,46] A detailed literature review of erythromycin-induced ototoxicity (with a case report) also can be found in Magata, et al.[47]

The World Health Organization (WHO), identified azithromycin to be most effective and safe to meet the most important needs in a country's health system.[48] The earliest reports of hearing loss from the use of azithromycin first appeared in 1993.[49] There are mixed reports of irreversible hearing loss,[50-54] reversible hearing loss after the drug is discontinued,[55-63] and no hearing loss during or after drug use.[64-69]

Mechanism of Action

Azithromycin works by decreasing the production of protein, thereby stopping bacterial growth.[70]

In the cochlea, there can be edema of stria vascularis (SV) in all turns, scattered loss of outer cochlear hair cells in the basal turn, mild apical atrophy of the spiral ligament and SV, and mild loss of cochlear neurons in the basal turn.[60] This supports the recommendation for distortion product optoacoustic emission (DPOAE) monitoring more regularly than pure tones.[59]

Azithromycin as an Adjunct with Hydroxychloroquine

Earlier in 2020, the coronavirus (SARS-CoV-2 also known as COVID-19) spread rapidly throughout the world. No vaccine exists to intercept this virus and the U.S. FDA requirements to prove a new or repurposed drug can take years. Even if a drug receives Emergency Authorization Use from the FDA it can still take over a year to complete the rigid clinical trials proving efficacy and safety.[5,71]

One drug, hydroxychloroquine—a derivative of chloroquine (which is a derivative of quinine)—has been used successfully for decades to treat malaria, lupus and rheumatoid arthritis and has been studied in African nations.[72-77] In five of those studies,[73-76] ototoxicity was not reported among a total of 1,708 participants. Cook, et al.[72] reported that the combination of azithromycin and chloroquine does not exhibit any direct pharmacokinetic interactions.

Li et al.[78] suggested that adding the antibiotic azithromycin as an adjunct to the hydroxychloroquine was suggested because of its antipurative properties.

As was seen earlier in this article, both drugs have ototoxic capabilities despite inconsistent reports regarding the same. However, when these two drugs are combined there are some concerns for both the physician and audiologist.

Along with common adverse effects including pruritus, nausea and headache, Juurlink[79] reported that 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.

The reader should check the National Library of Medicine's clinical trials website for updates on current research trials using these medications (www.clinicaltrials.gov).

Rutgers Cancer Institute of New Jersey is currently conducting a clinical trial for patients diagnosed with the coronavirus (COVID-19) to determine if azithromycin combined with hydroxychloroquine is better than hydroxychloroquine alone for treatment of patients with COVID-19.

The author received the following reply from the institute's Director, Steven K. Libutti, MD, FACS, when asked about any ototoxicity monitoring protocol in their current study. He commented,

> *The trial is designed to rapidly ascertain any anti-viral effect. If we demonstrate any activity of the agents alone or in combination, then exploring auditory concerns in future studies is certainly warranted. If they don't show any antiviral activity, it is my hope we will move in a different direction with respect to therapies.*

Unanswered Questions for Audiologists

With so much conflicting information in the media, along with inconsistencies in how these two drugs affect hearing short term and long term, the following questions need to be answered:

What is the synergistic effect (if any) when these two drugs are combined with a COVID-19 patient regardless of age or any co-morbidities?

Will any pre-existing hearing loss be permanently affected, temporarily affected or not affected at all?

Will tinnitus (new) or pre-existing tinnitus be exacerbated (temporary or permanent)?

What effect will these two drugs have on outer hair cell (OHC) function as it relates to DPOAE findings?

Will a reversed hearing loss still show evidence of OHC damage based on DPOAE monitoring?

How long should monitoring continue after the drugs are discontinued?

Audiological Management

Audiologists are in uncharted territory in managing COVID-19 survivors who were treated with hydroxychloroquine/cholorquine and azithromycin. Audiologists could possibly start seeing out-patient COVID-19 survivors with communication complaints from hearing loss – a loss that might possibly have occurred from their drug treatment regimen when they were hospitalized. Therefore, some management strategies are suggested:

Case History Questions: A new line of questions must be added that focuses on the patient's treatment regimen while hospitalized. A drug list is imperative.

Audiometric Testing Schedule: An audiometric testing protocol and schedule (outward to 12 months) can be similar for patients who will be or who have taken any platinum-based drug or an aminoglycoside antibiotic.

Baseline Testing: Baseline testing must include DPOAEs in addition to standard and high frequency audiometry. Word recognition tests (especially speech-in-noise testing) should be standard.

Tinnitus Evaluation: The Tinnitus Functional Index (TFI) and/or the Tinnitus Handicap Inventory (THI) should be included as needed and then quarterly.

Hearing Aids and Assistive Technology: When indicated, amplification and other assistive listening or alerting devices should be introduced.

Counseling: The usual individual or family counseling should be included or a referral made to a licensed professional if the patient's issues are beyond your counseling skills.

Summary and Conclusions

Audiologists have known about the ototoxicity of quinine (and its derivatives) and antibiotics (macrolide and

aminoglycoside) for decades. But we have never seen the combined use of two drugs, each with known ototoxic potential, being used as an intervention strategy for the coronavirus pandemic (COVID-19).

Published research and case reports (including one from the author's own patient files) about patients who were given hydroxychloroquine and/or azithromycin while hospitalized suggest that COVID-19 survivors could experience:

- No hearing loss
- Hearing loss that reverses to pre-treatment levels after the drug is discontinued
- Late onset of hearing loss after the drug is discontinued
- Full or partial recovery from hearing loss from one to four months later
- Tinnitus, depending on the degree of the loss but directly from the drug(s)

Management strategies for the audiology clinic will need to be developed that are similar to strategies used in ototoxic drug monitoring programs.

Recommendation

Although hearing loss incidence figures are low with hydroxychloroquine and azithromycin, the synergistic effects of these drugs on COVID-19 survivors are unknown. This unknown synergy will need to be identified and data compiled for further analysis. The results will not only add to the body of knowledge about this drug combination but also serve as a better guide for audiologists in managing COVID-19 survivors.

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Endnotes

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