COVID-19—Face Mask Effectiveness, Hand Sanitizer Shortages, and Rapid Medication Therapy Trials

Chris Alderman

The COVID-19 pandemic is a rapidly evolving phenomenon that presents serious practical challenges and complex clinical considerations for health care workers, health care administrators, and policy formulators. The Senior Care Pharmacist carries periodic updates addressing matters relevant to pharmacotherapeutics and pharmacy practice as these relate to the care of older people in the time of the pandemic. The brief news items that are provided here are not intended to be substitutes for a careful and comprehensive consideration of the issues involved, but rather, they serve to provide initial awareness of concepts and to stimulate more complete situational analysis.

KEY WORDS: Azithromycin, Colchicine, Hand sanitizer, Hydroxychloroquine, Ivermectin, Personal protective equipment.

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Protecting the Health of Frontline Workers—Are Face Masks Effective?

Korean researchers have recently undertaken a small, nonclinical research study to test the effectiveness of surgical and cotton masks in filtering the COVID-19 virus. The research compared disposable surgical masks and reusable 100% cotton masks. A petri dish of viral transport media was positioned 20 cm from infected patients’ mouths, and these people were instructed to cough five times onto a petri dish while wearing no mask, a surgical mask, a cotton mask, and again with no mask (a separate petri dish was used for each of the five coughing episodes). Mask surfaces were swabbed with aseptic Dacron swabs in the following sequence: outer surface of surgical mask, inner surface of surgical mask, outer surface of cotton mask, and inner surface of cotton mask. All swabs from the outer mask surfaces of the masks were positive for the virus; whereas, most swabs from the inner mask surfaces were negative. Neither surgical nor cotton masks effectively filtered the virus from coughing patients.

These findings are in contrast to previous evidence that suggested surgical masks could effectively filter other viruses such as influenza, and the researchers suggest that this is probably because of the different sizes of viral particles.

Of special note was the finding that contamination on the outer surface of the masks was greater than that on inner mask surfaces. The researchers hypothesized that a turbulent jet caused by air leakage around the mask edge might contaminate the outer surface, or that small aerosols of the virus created by a high-velocity cough could penetrate the masks, emphasizing the importance of hand hygiene after touching the outer surface of masks.

This experiment did not include N95/P2 masks, and it is highlighted that the study does not assess clinical virus transmission or effects of masks in shortening the trajectory of droplets generated by coughing. It appears that simple masks may be ineffective in
preventing the spread of the virus from the coughing patients to the environment. This benchtop research has potential ramifications for frontline health workers (including pharmacists) who might be relying on patients wearing masks as a means to prevent spread of the disease to those involved with providing care.

### Compounding Hand Sanitizer

The United States Pharmacopoeia has provided a regularly updated web page to address issues arising from shortages of alcohol-based hand sanitizers during the COVID-19 pandemic. The web page is a rich resource that links to a range of practical information, including:

- World Health Organization documentation that addresses local production of handrub formulations
- The US Food and Drug Administration (FDA) Policy for Temporary Compounding of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency
- Recommendations from the USP Compounding Expert Committee, providing three formulations for the compounding of hand sanitizer (including appropriate ingredient substitutions based on shortage issues), with options including a formulation using a starting ingredient of ethanol 96% for final product concentration of ethanol 80% (v/v), and alternative formulations using isopropyl alcohol 99% for final product concentration of isopropyl alcohol 75% (v/v) and isopropyl alcohol 91% for final product concentration of isopropyl alcohol 75% (v/v)

### Ivermectin in the News

Pharmacists might not have heard of the FDA-approved broad spectrum antiparasitic agent ivermectin because the conditions the drug is used to treat are relatively uncommon in nations with developed economies and because many practitioners may have worked an entire career without having seen an order for this drug. As a consequence of the desperate search for new therapeutic options for the treatment of COVID-19 infection, it appears that this lack of awareness might change.

**In vitro** research has suggested that ivermectin can inhibit the COVID-19 virus (also referred to as SARS-CoV-2). A recently published study found that this agent can produce an approximate 5,000-fold reduction in virus count in cell culture after 48 hours, with the researchers advocating for further investigation. However, results observed in a test tube may not necessarily translate into benefits for infected patients. For example, other research such as a recent phase III clinical trial of ivermectin as a treatment for dengue fever conducted in Thailand showed that though a single daily dose was found to be safe, this approach did not produce any clinical benefit.

This drug is indicated for use in the treatment of strongyloidiasis (infection with *Strongyloides stercoralis*) and onchocerciasis, and as a topical treatment for scabies. The drug is not approved for the treatment of COVID-19 infection. A previously published paper has drawn attention to serious neurological events as one of a number of important adverse reactions to this drug observed in clinical applications.

These neurological events in humans—clinically significant issues such as encephalopathy, confusion, stupor, or coma—were seen after ivermectin was used to treat *Onchocerca volvulus* infections in African countries. At this stage, it would appear that a rush to embrace ivermectin as a therapeutic option for the management of COVID-19 infection is indeed premature. The issue is raised here for pharmacists who might be asked about this drug.

### Hydroxychloroquine/Azithromycin—A Complex and Evolving Issue

Health care professionals directed a great deal of attention to the possible adoption of hydroxychloroquine +/- azithromycin for treating COVID-19 infections after early preclinical and early practical research suggested promise. To an extent, discussion has transcended the clinical sciences and has entered the political arena, and not all health care professionals are comfortable with this outcome. Much of the enthusiasm for this approach appears to stem from a small study conducted in France, where COVID-19 patients were treated with 600 mg hydroxychloroquine daily, and in some cases (depending on clinical presentation) azithromycin was added to the treatment. Viral load in nasopharyngeal swabs was found to be reduced among those receiving
treatment when compared with controls, and the average duration of carrier status was also lower than that reported elsewhere. When azithromycin was added to hydroxychloroquine, the treatment appeared to be more efficient.

It is largely unclear why the addition of an antibacterial antibiotic to a regimen based on an antimalarial should confer additional efficacy—some have speculated that the effect may arise from a pharmacokinetic interaction that results in higher serum concentrations of the antimalarial agent. Other conjecture surrounds the possibility that hydroxychloroquine may confer at least part of its effect from immunomodulation properties. At this stage, the science to properly inform a true mechanistic understanding is not forthcoming. Indeed, even the original publisher of the study, (research with a range of methodological shortcomings) has felt compelled to issue a statement addressing the controversy.

An official statement from the International Society of Antimicrobial Chemotherapy (ISAC) addresses concerns the scientific community has raised regarding the circumstances around the study’s publication, and the somewhat puzzling wording represents what appears to be an inherent internal contradiction. A co-author of the paper was, at the time of publication, the editor of the journal in which the report was published, prompting ISAC to point out that the author had no involvement in the peer review of the manuscript and had no access to information regarding its peer review.

A traditional, major, international clinical trial has now been launched: a randomized, open clinical trial assessing the safety and efficacy of various treatments for COVID-19 in hospitalized adults, comparing the usual standard of care (SoC) in the participating hospital with SoC + remdesivir OR SoC + lopinavir/ritonavir OR SoC + lopinavir/ritonavir plus interferon β-1a OR SoC + hydroxychloroquine.

In the meantime, the grave situation arising from the high mortality rate associated with COVID-19 appears to have prompted pre-emptive action around the world. Clinicians have started using these medications widely in clinical practice, and, in many cases, using them in parallel with recently commenced randomized trials. The prevailing philosophy appears to be “the perfect is the enemy of the good.” This implies that, given the urgency of the situation, to wait for the results of impeccable clinical trials will mean that many patients could die in the interim.

Another argument is that both hydroxychloroquine and azithromycin have been widely used in clinical practice for many years, suggesting that clinical safety data for both drugs does already exist. Even so, the parameters for the use of the drugs in the management of COVID-19 infections has many nuances.

Another concerning issue is that clinicians (including nonmedical clinicians such as dentists) may be self-prescribing the drug in some parts of the world, stockpiling supplies for themselves and for their families. The social equity issues that are implicit are complex—on the one hand, it can be argued that a privileged group within society should not have preferential access to the treatment by virtue of a conflict of interest; conversely, some suggest that no group is more exposed to the potential for COVID-19 infection than the doctors involved in treating patients. Because of this, perhaps these people should have the right to access treatment if they and their families become infected.

Given that azithromycin inhibits CYA-3A4, possibly slowing the metabolic clearance of hydroxychloroquine and accentuating the potential cardiotoxicity, safety concerns have been voiced about possible adverse effects. Moreover, in a relative vacuum of information derived from traditional sources (i.e., high-quality clinical trials), some clinicians advocate an approach that involves very-high-dose hydroxychloroquine treatment (such as 1,200 mg). Both drugs are implicated as iatrogenic causes of prolonged QT interval, which may result in the seriously dangerous cardiac rhythm disturbance, torsades de pointes. Overall, with respect to the possible adverse cardiac effects among a cohort of people already gravely ill, there are those that suggest that the “cure” (as yet not definitively proven) may be worse than the natural course of the disease itself. In response, attention is now turning to the issue of how to manage serious QTc prolongation associated with hydroxychloroquine/azithromycin, with guidance provided in various publications including a recent paper that includes a useful algorithm.
Colchicine—the Next Hope for Treatment?

Meanwhile, a clinical trial has been initiated in Canada to determine if colchicine can improve outcomes for people with COVID-19. Referred to as the COLCORONA study, this research will evaluate whether the drug can prevent a cytokine storm, an immune system reaction seen in some people with severe sequelae of COVID-19 infection. Initiated in Montreal, Canada and now expanded to New York City, the plan is to recruit 6,000 participants and follow these people for 30 days. The premise for the study arose from the observation of the positive effects of the anti-inflammatory actions of the drug in the period following myocardial infarction (in other studies). To participate, subjects must test positive for COVID-19, be 40 years of age or older, have at least one high-risk criterion, and must take the colchicine or placebo daily for 30 days, with follow-up calls by phone or videoconference.

Conclusion

While the COVID-19 situation continues to unfold, The Senior Care Pharmacist will continue to carry updates to inform the readership about developments. Questions, comments, and suggestions can be sent directly to calderman@ascp.com.

Chris Alderman, B Pharm, PhD, FASCP, FSHP, BCGP, BCPP
Editor-in-chief of The Senior Care Pharmacist.