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In Vitro Efficacy of a Povidone-Iodine Nasal Antiseptic for Rapid Inactivation of SARS-CoV-2

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IMPORTANCE Research is needed to demonstrate the efficacy of nasal povidone-iodine (PVP-I) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

OBJECTIVE To evaluate the in vitro efficacy of PVP-I nasal antiseptic for the inactivation of SARS-CoV-2 at clinically significant contact times of 15 and 30 seconds.

INTERVENTIONS The SARS-CoV-2, USA-WA1/2020 strain, virus stock was tested against nasal antiseptic solutions consisting of aqueous PVP-I as the sole active ingredient. Povidone-iodine was tested at diluted concentrations of 0.5%, 1.25%, and 2.5% and compared with controls. The test solutions and virus were incubated at mean (SD) room temperature of 22 (2) °C for time periods of 15 and 30 seconds.

DESIGN AND SETTING This controlled in vitro laboratory research study used 3 different concentrations of study solution and ethanol, 70%, as a positive control on test media infected with SARS-CoV-2. Test media without virus were added to 2 tubes of the compounds to serve as toxicity and neutralization controls. Ethanol, 70%, was tested in parallel as a positive control and water only as a negative control.

MAIN OUTCOMES AND MEASURES The primary study outcome measurement was the log reduction value after 15 seconds and 30 seconds of given treatment. Surviving virus from each sample was quantified by standard end point dilution assay, and the log reduction value of each compound was compared with the negative (water) control.

RESULTS Povidone-iodine nasal antiseptics at concentrations (0.5%, 1.25%, and 2.5%) completely inactivated SARS-CoV-2 within 15 seconds of contact as measured by log reduction value of greater than 3 $\log_{10}$ of the 50% cell culture infectious dose of the virus. The ethanol, 70%, positive control did not completely inactivate SARS-CoV-2 after 15 seconds of contact. The nasal antiseptics tested performed better than the standard positive control routinely used for in vitro assessment of anti–SARS-CoV-2 agents at a contact time of 15 seconds. No cytotoxic effects on cells were observed after contact with each of the nasal antiseptics tested.

CONCLUSIONS AND RELEVANCE Povidone-iodine nasal antiseptic solutions at concentrations as low as 0.5% rapidly inactivate SARS-CoV-2 at contact times as short as 15 seconds. Intranasal use of PVP-I has demonstrated safety at concentrations of 1.25% and below and may play an adjunctive role in mitigating viral transmission beyond personal protective equipment.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus resulting in coronavirus disease 2019 (COVID-19), is a novel coronavirus in the same family as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome. High viral loads of SARS-CoV-2 have been detected in the nasopharynx and oropharynx of symptomatic patients and asymptomatic carriers.[1] Nasal goblet and ciliated cells have the highest expression of angiotensin-converting enzyme 2 (ACE2), which is the main receptor for SARS-CoV-2.[2] Many otolaryngologic procedures may produce aerosols that can last in the air for up to 3 hours without rapid filtration.[3-5] Recently, Hou et al[6] showed that ciliated cells with ACE2 expression were the cells most susceptible to infection, rather than submucosal glandular cells. The infectivity of these cells was much higher than that of lower airway cells. This study highlighted a virus transmission pathway that involves infection of ciliated cells of the upper airway within the nose as the dominant site of infection, followed by subsequent aspiration and seeding of the lungs. The nasal-oropharyngeal axis involves nasal secretions swept to the oropharynx by mucociliary clearance followed by aspiration of infected fluid into the lower airway. It is hypothesized that this upper-lower airway route may explain the observed differences between detection, persistence of viral load, and transmission dynamics seen between previous SARS-CoV outbreaks and the current COVID-19 pandemic. It is thought that this process may also play a role in the variable expression of clinical severity.[7] Of note, a recent work[8] on the transmission dynamics for influenza A also provides an example of this nasal-oropharyngeal axis with subsequent seeding of the lungs leading to respiratory disease.

Transmission reduction in the otolaryngology community has mainly focused on the use of physical barriers and personal protective equipment. Masks have become a standard form of personal protective equipment almost universally adopted in the health care setting for the protection of patients, staff, and health care professionals. Nasal decontaminants have been advocated to sterilize the nasal cavity in patients and health care workers to mitigate transmission. Multiple protocols have come forth recommending intranasal use of povidone-iodine (PVP-I) in patients and health care workers.[9-12] Povidone-iodine was selected given its proven in vitro efficacy against SARS-CoV and Middle East respiratory syndrome at concentrations as low as 0.23%.[13,14] In vitro efficacy of an oral PVP-I antiseptic solution was recently demonstrated specifically against SARS-CoV-2 at concentrations as low as 0.5% for contact times as short as 15 seconds.[15] We aim to investigate the in vitro efficacy of an intranasal preparation of PVP-I against SARS-CoV-2 at various concentrations and contact times to inform its use by the otolaryngology community in the clinic and operating room setting for viral transmission mitigation.

Key Points

Question What is the minimum contact time of povidone-iodine (PVP-I) nasal antiseptic required for inactivation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro?

Findings In this controlled in vitro laboratory research study, test media infected with SARS-CoV-2 demonstrated complete inactivation of SARS-CoV-2 by concentrations of PVP-I nasal antiseptic as low as 0.5% after 15 seconds of contact, as measured by a log reduction value of greater than 3 $\log_{10}$ of the 50% cell culture infectious dose of the virus.

Meaning Intranasal PVP-I rapidly inactivates SARS-CoV-2 and may play an adjunctive role in mitigating viral transmission beyond personal protective equipment.

Methods

All laboratory work with SARS-CoV-2 was conducted in biosafety level 3 laboratories at the Institute for Antiviral Research at Utah State University following established standard operating procedures approved by the Utah State University Biohazards Committee. The Utah State University Institutional Review Board approved this study. The SARS-CoV-2, USA-WA1/2020 strain, virus stock was prepared prior to testing by growing in Vero 76 cells. Culture media for prepared stock (test media) were minimum essential medium with 2% fetal bovine serum and 50 µg/mL gentamicin. The nasal rinse antiseptic solution consisted of various concentrations of aqueous PVP-I as the sole active ingredient (Veloce BioPharma). The PVP-I concentrations of each solution as supplied and after 1:1 dilution are summarized in **Table 1**. The test compounds were mixed directly with virus solution so that the final concentration was 50% of each individual test compound and 50% virus solution. A single concentration was tested in triplicate. Test media without virus were added to 2 tubes of the compounds to serve as toxicity and neutralization controls. Ethanol 70% was tested in parallel as a positive

Table 1. Virus Titers and Log Reduction Value (LRV) of SARS-CoV-2 When Incubated With Various Concentrations of Povidone Iodine (PVP-I) and Controls for 15 Seconds

Test product	PVP-I concentration after 1:1 dilution, %	Virus titer[a]	LRV[b]
PVP-I nasal antiseptic			
5.0%	2.5	<0.67	3.0
2.5%	1.25	<0.67	3.0
1.0%	0.50	<0.67	3.0
Ethanol 70%	NA	1.5	2.17
Virus control	NA	3.67	NA

Abbreviations: $CCID_{50}$, 50% cell culture infectious dose; NA, not applicable; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] $\log_{10}$ $CCID_{50}$ of virus per 0.1 mL. The assay lower limit of detection is 0.67 $\log_{10}$ $CCID_{50}$/0.1 mL.

[b] Log reduction value is the reduction of virus compared with the virus control.

Table 2. Virus Titers and Log Reduction Value (LRV) of SARS-CoV-2 When Incubated With Various Concentrations of Povidone Iodine (PVP-I) and Controls for 30 Seconds

Test product	PVP-I concentration after 1:1 dilution, %	Virus titer[a]	LRV[b]
PVP-I nasal antiseptic			
5.0%	2.5	<0.67	3.33
2.5%	1.25	<0.67	3.33
1.0%	0.50	<0.67	3.33
Ethanol 70%	NA	<0.67	3.33
Virus control	NA	4.0	NA

Abbreviations: $CCID_{50}$, 50% cell culture infectious dose; NA, not applicable; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2.

[a] Log_{10} $CCID_{50}$ of virus per 0.1 mL. The assay lower limit of detection is 0.67 log_{10} $CCID_{50}$/0.1 mL.

[b] Log reduction value is the reduction of virus compared with the virus control.

control and water only as a negative control. The test solutions and virus were incubated at mean (SD) room temperature 22 (2) °C for 15 and 30 seconds. The solution was then neutralized by a 1/10 dilution in minimum essential medium, 2% fetal bovine serum, 50 µg/mL gentamicin. Surviving virus from each sample was quantified by standard end point dilution assay. The neutralized samples were pooled and serially diluted using 8 log dilutions in test medium. Then 100 µL of each dilution was plated into quadruplicate wells of 96-well plates containing 80% to 90% confluent Vero 76 cells. The toxic effect controls were added to additional 4 wells of Vero 76 cells, and 2 of those wells at each dilution were infected with the virus to serve as neutralization controls, ensuring that residual sample in the titer assay plate did not inhibit growth and detection of surviving virus. Plates were incubated at a mean (SD) temperature of 37 (2) °C with 5% carbon dioxide for 5 days. Each well was then scored for presence or absence of infectious virus. The titers were measured using a standard end point dilution 50% cell culture infectious dose ($CCID_{50}$) assay calculated using the Reed-Muench equation, and the log reduction value (LRV) of each compound compared with the negative (water) control was calculated.[16]

Results

Virus titers and LRV of SARS-CoV-2 when incubated with various concentrations of the manufacturer's compounds for 15 seconds are summarized in Table 1. After the 15-second contact time, all of the PVP-I nasal rinse antiseptics tested were effective at reducing greater than 3 log_{10} $CCID_{50}$ infectious virus, from 3.67 log_{10} $CCID_{50}$/0.1 mL to 0.67 log_{10} $CCID_{50}$/0.1 mL or less. **Table 2** summarizes the virus titers and LRV of SARS-CoV-2 when the virus was incubated for 30 seconds with each of the test compounds at a 50/50 ratio. For the 30-second contact time, all of the PVP-I nasal rinse antiseptics tested were effective at reducing greater than 3.33 log_{10} $CCID_{50}$ infectious virus, from 4.0 log_{10} $CCID_{50}$/0.1 mL to 0.67 log_{10} $CCID_{50}$/0.1 mL or less. No cytotoxic effects were observed with any of the test compounds. The positive control was effective at reducing greater than 3 log_{10} $CCID_{50}$ infectious virus at 30 seconds, which is comparable with the PVP-I nasal rinse antiseptics. However, at 15 seconds of contact, the positive control was effective at reducing only 2.17 log_{10} $CCID_{50}$ infectious virus, which is less effective than the PVP-I nasal rinse antiseptics. The negative control with water only was not at all effective at reducing virus load.

Discussion

This study demonstrates rapid inactivation of SARS-CoV-2 by PVP-I at concentrations as low as 0.5% for as little as 15 seconds of contact. These findings are consistent with those of a previous study investigating efficacy of an oral solution in the same class of PVP-I antiseptics against SARS-CoV-2.[15] Solutions of PVP-I are known to have concentration-dependent effects on ciliary beat frequency (CBF) when studied in model in vitro systems.[17] In experimental models, PVP-I solutions up to 1.25% did not demonstrate inhibitory effects on CBF. This suggests that PVP-I solutions up to 1.25% would be well tolerated by the nasal epithelium for short-term use.[17,18] Clinical studies have demonstrated that lower concentrations can be administered acutely and over a period of months with no adverse effects.[19] Repeated use of dilute 0.08% PVP-I every other day in patients with chronic rhinosinusitis for up to 7 weeks did not result in any adverse effects on mucociliary clearance or olfaction.[20,21] When administered intranasally in humans, there is an effective dilution of the applied formulation as it is immediately combined with the existing nasal secretions.[22] In addition to the 95% aqueous component of the nasal secretions, intranasally applied PVP-I also encounters mucin products released from goblet cells and submucosal glands including glycoproteins, proteoglycans, and lipids. There are also physiologic buffers, extracellular remnants of degenerating cells, and fragments of extracellular nucleic acids. All of this biological debris can act as an iodine sink and can lower the effective concentration of PVP-I delivered to the site of infection.[23,24] For these reasons, it is important to choose PVP-I concentrations below the threshold of in vitro CBF impairment but above the minimum effective biocidal level to account for iodine consumption and physiological buffering. We have implemented the use of intranasal PVP-I in our practice and have updated all of our protocols to include use of 1.25% aqueous PVP-I formulations delivered to each nasal cavity in patients before any intranasal procedure.

This study demonstrates that a contact time of 15 seconds is sufficient for viral inactivation. Widespread use of PVP-I nasal antiseptic in patients prior to intranasal procedures could significantly decrease risk of virus transmission via droplet and aerosol spread. Health care professionals may also consider instructing patients to perform nasal decontamination with PVP-I prior to presenting for their procedure, which can further decrease intranasal viral load and can prevent spread in waiting areas and other common areas.

Nasal PVP-I irrigations should additionally be considered for use by health care professionals for prophylaxis. Oral mucosa decontaminated with PVP-I remains sterilized for up to 4 hours.[25] Although this has not yet been proven in nasal mucosa, health care providers should consider use every 4 hours, or whenever donning or doffing a mask in high risk settings, up to 4 times daily. At concentrations of 1.25%, iodine absorption is negligible. These simple, nonbuffered, slightly acidic, complexed PVP-I solutions would further limit any transmucosal absorption of molecular iodine, providing only a minimal theoretical risk of iodine absorption. Even if some noncomplexed iodine were absorbed transmucosally, it would still be orders of magnitude less than the average total daily iodine intake for a healthy adult of 150 µg.[19] Use of 0.08% nasal PVP-I every other day for up to 7 weeks does not result in clinical thyroid disease.[20,21] Nevertheless, thyroid function testing should be considered when PVP-I is regularly administered to patients for more than 3 months. Use of intranasal PVP-I is contraindicated in patients with an allergy to iodine, patients who are pregnant, patients with active thyroid disease, and patients undergoing radioactive iodine therapy.[26-28]

Limitations

Randomized clinical trials have not yet been conducted to prove that viral transmission is mitigated with intranasal use of PVP-I, although these studies are already under way. Similarly, the safety of intranasal PVP-I use in regard to thyroid-stimulating hormone, olfaction, and mucociliary clearance has only specifically been demonstrated at concentrations up to 0.08% for a time period of up to 7 weeks. Safety has been inferred based on in vitro studies, but in vivo tolerability trials proving safety of PVP-I up to 1.25% for long-term use are currently underway. Health care professionals should either use commercially available PVP-I solutions in the appropriate concentration range or use freshly prepared dilute solutions of their own. Caution is advised when diluting commercial preparations, as many contain detergents, buffers, counterions, alkalinizing agents, surfactants, and other chemical excipients, which may not have been studied or approved for intranasal application. Most common antiseptic product formulations intended for keratinized skin surfaces, including many PVP-I presurgical scrubs and preparation kits, may contain excipients and additives that can be toxic when administered intranasally.[29,30] Freshly diluted solutions should be prepared each day, refrigerated during the day, and discarded immediately at the end of each day. Commercial PVP-I solutions at 5% to 10% aqueous concentrations can become chemically unstable when simply diluted to lower concentrations with additional water, saline, or other common clinical solvents. Aqueous and alcoholic PVP-I solutions are unstable at low concentrations. They readily engage in unpredictable disproportionation reactions into constituent equilibrium species with sensitive dependence on pH, temperature, exposure to light, counterion content, packaging material, atmospheric pressure, copolymer content, and a myriad of other factors that may be difficult for an individual health care professional to control. In order to ensure that a dilute solution prepared from a high-concentration (ie, 5%-10%) PVP-I product is safe for administration to the nasal cavity, there should be an analysis of the chemical ingredients of each freshly prepared solution according to the United States Pharmacopeia method for PVP-I assay,[31] or only commercial preparations of PVP-I at the appropriate dose (if available) should be employed.

Conclusions

Hou et al[6] recently demonstrated that SARS-CoV-2 initially infects ciliary cells of the nasal mucosa and that this may represent the dominant initial site for infection. The virus then spreads via the nasal-oropharyngeal axis to the lungs through microaspiration, leading to the damaging respiratory infections seen in COVID-19. The variable severity witnessed during the COVID-19 pandemic may be due to variable transmission of SARS-CoV-2 from the nasal cavity to the lungs in patients who test positive for the virus. Therefore, transnasal viral inactivation may not only prevent person-to-person spread of SARS-CoV-2, but may also diminish the severity of disease in patients by limiting spread and decreasing viral load delivered to the lungs. Povidone-iodine nasal irrigation may be beneficial for the population at large as an adjunct to mask usage as a means of virus mitigation.

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Acquisition, analysis, or interpretation of data: Frank, Capriotti, Westover, Tessema.
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Conflict of Interest Disclosures: Dr Brown reported personal financial investment in Halodine outside the submitted work. Dr Capriotti is the executive director of Veloce BioPharma and reported a patent to multiple related drugs issued and licensed by Veloce BioPharma. Dr Pelletier is a consultant for Veloce BioPharma and reported equity in both Veloce BioPharma and Halodine. Dr Tessema reported personal financial investment in Halodine outside the submitted work, and has a patent to multiple drug products pending. No other disclosures were reported.

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