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ABSTRACT (WHITE JOURNAL FORMAT)

Objective: To provide a state-of-the-art review of intranasal antiviral drug delivery and to discuss current applications, adverse reactions, and future considerations in the management of Coronavirus Disease (COVID-19).


Review Methods: A structured search of the current literature was performed of dates up to and including April 2020. Search terms related to topics of antiviral agents and intranasal applications were queried. A series of video conferences was convened of experts in otolaryngology, infectious diseases, public health, pharmacology, and virology to review the literature and discuss relevant findings.

Conclusions: Intranasal drug delivery for antiviral agents have been studied for many years. Several agents have broad-spectrum antiviral activity, but they still require human safety and efficacy trials prior to implementation. Intranasal drug delivery has potential relevance for future clinical trials in the settings of disease spread prevention and treatment of SARS-CoV-2 and other viral diseases.

Implications for Practice: Intranasal drug delivery represents an important area of research for COVID-19 and other viral diseases. The consideration of any potential adverse reactions is paramount.
INTRODUCTION

The rapid spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the immunologically naïve human population has led to a global pandemic. SARS-CoV-2 is spread primarily through airborne droplet and contact transmission with contaminated fomites. While SARS-CoV-2 particles may persist on surfaces for several days, as enveloped viruses, they are sensitive to desiccation and mild detergent disinfection. Small population studies indicate that between 6% and 88% of SARS-CoV-2 infections do not result in overt disease. The impact of asymptomatic or subclinical individuals to public health is clear, with up to 44% of infected individuals having contracted the virus from asymptomatic persons. Individuals who display clinical symptoms of SARS-CoV-2 infection, or coronavirus disease (COVID-19), exhibit a range of symptom severity, with high case fatality rates in the elderly, immunocompromised patients, or those with comorbid diabetes, cardiac, pulmonary, and immunocompromised conditions.

The nasal cavity and nasopharynx contain some of the highest viral loads in the body, and viral loads are similar in symptomatic and asymptomatic individuals. Accordingly, these “silent spreaders” may unknowingly contribute to the exponential growth of disease as nasal secretions contain spreadable virus, and contagiousness appears to be highest before or shortly after symptom onset.

Current strategies to mitigate the pandemic have focused on public health initiatives, such as social distancing, community hygiene awareness, testing and tracing, and travel restrictions. Intranasal delivery of antiviral drugs or agents may provide an additional option for preventing disease transmission, treating the nasal disease, and providing perioperative
Intranasal Antiviral Agents and COVID-19

This article summarizes our findings for the potential role of studying topical intranasal delivery of drug and agents known to have antiviral properties in SARS-CoV-2.

METHODS

A search of PubMed, Embase, and clinicaltrials.gov was conducted to identify relevant peer-reviewed English articles related to intranasal application of drugs and agents with antiviral properties. A multidisciplinary team of specialists in the areas of otolaryngology, infectious diseases, public health, pharmacy, and virology was assembled to review and summarize the literature. A series of video conferences were held to interpret the findings and discuss potential applications of intranasal application of antiviral agents in the setting of the COVID-19 pandemic. The panel discussed several topics relevant for consideration in intranasal antiviral drug therapy (Figure 1). Agents were assessed for evidence of antiviral activity, either in SARS-CoV-2 and other viruses, and efficacy or potential feasibility in human intranasal use. Potential intranasal adverse reactions were evaluated—specifically—mucosal or skin irritation, smell and taste disturbance, headaches, allergic reactions, nasal bleeding, fungal infection or colonization, and rhinosinusitis. Additional items of discussion included adequacy of mechanisms of target or viral cell infiltration, routes of delivery, medium suspension, additives to enhance mucosal or cellular absorption of the agents, and the reliability of compounding these substances.

DISCUSSION

Viral Structure and Mechanism

Coronaviruses, such as SARS-CoV-2, are enveloped positive-sense RNA viruses with a genome length of approximately 30k nucleotides encoding 16 nonstructural proteins, and at least
4 main structural proteins, although the absolute number varies amongst the members of Coronavirinae (Figure 2). Coronaviruses, such as SARS-CoV-2, are enveloped positive-sense RNA viruses with a genome length of approximately 30k nucleotides encoding 16 nonstructural proteins, and at least 4 main structural proteins, although the absolute number varies amongst the members of Coronavirinae. Architecturally, coronavirus particles are spherical with an average diameter of 125 nanometers, from which the projection of the Spike glycoproteins create a crown-like appearance responsible for the name of the genus. In addition to the Spike glycoproteins, coronavirus particles consist of the E and M integral membrane proteins, a host-derived lipid envelope, and the helical viral nucleocapsid consisting of the N protein and the viral genomic RNA.

As summarized in Figure 3, the coronavirus cellular viral life cycle begins with the attachment of the viral particle to the host cell via the viral Spike glycoprotein. SARS-CoV-2 utilizes the human Angiotensin-Converting Enzyme 2 (hACE2) protein as its primary receptor for viral entry. The coronavirus cellular viral life cycle begins with the attachment of the viral particle to the host cell via the viral Spike glycoprotein. The cellular receptor involved in viral entry varies amongst the members of Coronavirinae; however, the SARS-CoV-2 virus, in addition to the original SARS virus (SARS-CoV-1) and the endemic human coronavirus HCoV-NL63, utilize the human Angiotensin-Converting Enzyme 2 (hACE2) protein as its primary receptor. The entry of the virus into the host cytoplasm requires a series of two proteolytic cleavage events of the Spike glycoprotein to reveal the fusion peptide which mediates the fusion of the viral and cellular lipid bilayers. The delivery of the viral RNA into the cytoplasm results in the expression of the viral replicase complex, which consists of 16 nonstructural proteins encoded by the genomic RNA. Within the viral replication compartment, viral RNA synthesis
produces a nested set of mRNA transcripts produced via a complex discontinuous RNA synthesis mechanism, which produces complementary negative sense RNA templates. The nested mRNAs produce the remainder of the viral structural proteins, and progeny viral genomes are produced by way of continuous viral RNA synthesis. The formation of new viral nucleocapsids occurs in the cytoplasm of the infected cells, and mature viral particles are budded into the Endoplasmic Reticulum-Golgi Intermediate Complex (ERGIC) via an interaction between the ERGIC membrane associated M protein and the N protein of the nucleocapsid. The mature viral particles are trafficked to the cell membrane in smooth walled vesicles and released to the extracellular space.

To date, seven CoVs capable of infecting humans have been identified and account for 5% to 10% of acute respiratory infections. Most endemic CoVs cause self-limiting upper respiratory infections; however, SARS-CoV, SARS-CoV-2, and Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) have notably high mortality rates. Transmission of SARS-CoV-2 appears to occur primarily through respiratory droplets, with secondary surface contact transmission and aerosol transmission possible. The incubation time is typically 3 to 7 days with up to 2 weeks between time of infection and symptoms. This long asymptomatic phase is thought to contribute to the large basic reproduction number (R0) of 2.5 to 3. Viral shedding has been detected in multiple anatomic sites, including the nasal cavities, nasopharynx, sputum, oropharynx, bronchial fluid, and stool. However, the nasopharynx had a much higher detection rate than the oropharynx.
Agents with Antiviral Capability

While no drug has been developed to specifically treat the SARS-CoV-2 virus, a few agents have been found to inactivate SARS-CoV-2 on surfaces, including ultraviolet radiation, heat, ether, ethanol, and isopropanol. Other agents have been studied with other viruses. Table 1 shows a summary of the antiviral agents discussed.

Alcohol and Isopropanol

The World Health Organization (WHO) hand hygiene in healthcare guidelines contain two alcohol-based formulations, including ethanol and isopropanol. These compounds are fast-acting, inexpensive, and broad-spectrum, previously showing the ability to inactivate both SARS-CoV and MERS-CoV. WHO recommends the use of at least 60% ethanol or 70% isopropanol in hand sanitizer formulations. Although, there is evidence that both alcohols inactivate the SARS-CoV-2 down to a concentration of 30%.

Intranasal application of alcohol formulations has been studied in a placebo-controlled RCT of 387 healthcare workers. Health care workers colonized with nasal S. aureus were swabbed intranasally three times a day with 70% ethanol combined with natural oil emollients and the preservative benzalkonium chloride or placebo. Antiseptic use reduced S. aureus colony forming units by a median of 99% (P<0.001) compared with placebo. The participants reported no adverse effects during the study.

Povidone-Iodine

Povidone-iodine (PI) has rapid bactericidal and virucidal activity, including against SARS-CoV and MERS-CoV. It is widely available in the clinical settings and has been utilized as a skin disinfectant as well as an oral wash or gargle rinse. 3M developed and evaluated an intranasal formulation (PI solution 5% w/w [0.5% available iodine] USP) application to the
anterior nares. A blinded expert grader assessment of the level of intranasal skin erythema and edema in 30 patients demonstrated no significant irritation by the Draize scale. Formulations of 5-10% PI have been evaluated intranasally with regards to potential side effects and results have shown no gross injury though ciliotoxicity has been demonstrated in vitro at these concentrations.\textsuperscript{20} A randomized control trial (RCT) of nasal application of 10\% PI, 5\% PI, or placebo preoperatively for arthroscopic surgeries for methicillin-resistant staphylococcus aureus (MRSA) prophylaxis found equal rates of nasal irritation.\textsuperscript{21} However, another study of 5\% and 10\% PI applied to ciliated human respiratory epithelial cells showed ciliotoxicity.\textsuperscript{22} Lower concentration formulations (0.5\% povidone-iodine [Nasodine]) applied in vitro to air-liquid interface cultures of primary human nasal epithelial cells was found to lack cytotoxicity or ciliotoxic effect.\textsuperscript{23} Calls for the consideration of PI application intranasally or orally has been advocated as a preventative for patients and healthcare workers involved in head and neck oncologic care at risk of COVID-19 exposure.\textsuperscript{24,25} A search of clinicaltrials.gov reveals that a few initiated protocols evaluating intranasal or intraoral formulations of PI for SARS-CoV-2.\textsuperscript{26-29}

\textit{Carrageenan}

Carrageenan is a polysaccharide food additive extracted from red seaweed extract widely used as a thickening agent for food. In vitro and animal studies demonstrate that carrageenan shows antiviral properties to human rhinovirus and influenza A and prevents viral attachment to host cells without systemic absorption or nasal mucosal penetration. Four placebo-controlled RCTs have been performed evaluated iota-carrageenan nasal spray in the treatment of respiratory viral infections (including rhinovirus, enteroviruses, and influenza) with variable reduction in symptoms and viral loads versus placebo saline spray.\textsuperscript{30,31} Formulations of nasal sprays...
containing carrageenan are available over the counter, but the FDA currently has only approved
this agent as a food additive permitted for human consumption.

**Acid-Buffered Saline**

Acidic pH is frequently used for virus inactivation. Acidic solutions are commonly used
in the pharmaceutical industry to inactivate viruses in the isolation of viral proteins and also for
cleaning and prevention of infection. Acid-buffered saline has been investigated as a topical
therapy for various upper respiratory viruses, showing inactivation of influenza A, decreased
symptoms and viral shedding of influenza A, reduced viral shedding of human rhinovirus with
the use of solutions and nasal gels, and reduced symptom severity and duration of illness in the
common cold. Unfortunately, SARS-CoV-2 has been shown to be highly stable in a wide
range of pH environments, limiting the viability of acidic therapies as options against this virus.

**Hypertonic Saline**

Hypertonic saline may reduce symptoms of various upper respiratory viruses, as well as
potentially reduce viral shedding and promote inactivation. Ramalingam et al. demonstrated
via *in vitro* studies that increasing the availability of NaCl may facilitate the innate immune
response in non-myeloid cells via an increase in intracellular hypochlorous acid levels.
Ramalingam et al. found in an RCT of hypertonic saline irrigation and gargling for the common
cold that the use of hypertonic saline reduced symptom severity, length of illness, intrahousehold
transmission, and viral shedding. Meta-analyses have shown good tolerability with some
reports of nasal irritation, headache, and epistaxis.
Hydrogen peroxide

Hydrogen peroxide (H$_2$O$_2$) has long been known to cause viral inactivation and H$_2$O$_2$ efficiently deactivates SARS-CoV-2 on surfaces. While H$_2$O$_2$ is commonly used for surface, surgical, and oral disinfection, there are currently no human clinical trials demonstrating the safety or efficacy of intranasal application of H$_2$O$_2$.

Probiotics

The use of ingested oral probiotics has been evaluated in the current COVID-19 pandemic, but the evidence of its use are from small case series and correspondences, and experts concluded that even if oral probiotics were useful, they were unlikely to have a direct effect on the severe acute respiratory syndrome that most patients with COVID-19 present with acutely. However, there is evidence that both the nasal and gastrointestinal microbiome are important factors in the innate immune system and, particularly, in the defense against respiratory viral pathogens. Nasal microbiota clusters were found associated with host inflammatory response, viral load, and symptom severity in rhinovirus. The *Corynebacterium*-rich cluster of patients had overall reduced symptoms during rhinovirus infection despite the addition of oral probiotics not changing the host microbiome (nasal and gastrointestinal) significantly. *Corynebacterium* was also found to be protective against Respiratory Syncytial Virus (RSV) infection in an *in vivo* mouse model. Also, in a mouse model, Zelaya et al. found that *Lactobacillus* introduced nasally helped prevent influenza pulmonary damage and inflammation. While the effects of orally administered probiotics on a variety of viruses has been studied, we found no studies directly investigating the introduction of intranasal probiotics for the treatment of human upper respiratory virus infections. Further studies on both nasal and
oral administration of probiotics are warranted for COVID-19 and other upper respiratory viral
infections.

**Surfactants/Shampoo**

Surfactants and, in particular, baby shampoo have been studied most extensively in
chronic rhinosinusitis. Most studies have evaluated potential bactericidal and anti-biofilm
effects. We found no studies that evaluated evaluating surfactant application to the nasal cavity
and its ability to prevent or diminish viral infection. However, intrinsic pulmonary surfactant has
been found to be an important part of our innate immune system, and its use has recently been
shown to help prevent several respiratory viruses such as H1N1 and influenza. The
pulmonary surfactant phospholipids are thought to prevent viral infections by inhibiting viral
binding to epithelial cells. The use of surfactants to achieve the same results in the upper
aerodigestive tract is intriguing but has not been studied. One proposed trial aims to investigate
the effect of saline irrigations and baby shampoo/saline irrigations on COVID-19 patients. Most surfactants have been reported to have good tolerability, but it is worthy to note that
surfactant additive in nasal saline rinses has been associated with nasal congestion and temporary
smell loss in normal volunteers.

**Ultraviolet Radiation**

Based on the physiologic effects, UV radiation can be divided into: UVC (100–280 nm),
UVB (280–320 nm) and UVA (320–400). The majority of evidence of the biological effect of
UV light has come from the field of dermatology, where various forms of phototherapy have
been applied for decades.
Intranasal phototherapy has been explored for the treatment of other rhinologic conditions, primarily based on its immunomodulating effect on inflammatory processes. Two RCTs demonstrated that combined low dose UVB, low dose UVA, and visible light are effective in reducing symptoms scores of moderate to severe ragweed-induced allergic rhinitis uncontrolled by anti-allergic drugs. However, a similar treatment protocols does not appear to have efficacy for treatment effective for of chronic rhinosinusitis.

The carcinogenic risk of rhinophototherapy on the nasal mucosa appears to be limited at the exposure levels used in the studies above. Nasal epithelial cells are capable of repairing UV-induced DNA damage in allergic rhinitis patients receiving intranasal phototherapy. Significant DNA damage was observed immediately after completing two weeks treatment of which reduced at the day-10 assessment and but was equivalent to the control group at 2-month follow-up. Parallel experiments demonstrated similar repair kinetics in human skin in vitro and animal models. Animal studies with UV-A and UV-B irradiation demonstrate no histopathological changes, and no induction of apoptosis at lower doses. Other animal studies have demonstrated similar reduction in histopathological changes with phototherapy compared to nasal corticosteroid treatment without increasing apoptosis of mucosal cells.

UV-C is strongly absorbed by the nucleic acids of a microorganism and, therefore, is the most lethal range of wavelengths for microorganisms. UV-C sterilization has been proposed as an effective method for simultaneous disinfection of both the water source and saline irrigation bottle, and has been used in combination to reduce titers of SARS-CoV-2 to non-detectable levels in human blood transfusion products.
Multiple clinical studies dating back to the 1940s\textsuperscript{61} demonstrate that UV exposure of the wound during surgery resulted in markedly decreased SSI rates. However, conventional UV-C light sources, typically emitting at 254 nm, are a human health hazard, causing skin cancer and cataracts.\textsuperscript{62,63} In contrast, far-UVC light in the range of 207–222 nm has the same bactericidal potential of 254-nm light, but without the damaging effects to mammalian cells and tissues. Due to its short range in biological materials, far-UVC light does not penetrate the outer layer of the skin or the outer surface of the eyes but can efficiently inactivate the nucleic acids and proliferative capacity of surface microbes.\textsuperscript{64,65}

While intranasal UV-A and UV-B light is safe, phototherapy at this wavelength has limited antimicrobial activity. UVC light is an effective method for sterilization, but the intranasal safety profile for UV-C phototherapy has not been studied.

**Oxymetazoline and Xylometazoline**

Oxymetazoline and xylometazoline are commonly using over-the-counter nasal decongestants. Adverse effects include local irritation and rhinitis medicamentosa in which overuse causes paradoxical nasal obstruction. Small studies have shown transient decreased viral load in rhinovirus utilizing topical oxymetazoline nasal spray.\textsuperscript{66} These agents have not been studied in other viruses or SARS-CoV-2. Given that it has been shown to reduce rhinovirus viral load, caution may be advisable with its use prior to nasal swab viral testing.

**Interferon**

Interferons are complex cytokines intricately involved in innate cellular immunity and are named for their ability to interfere with viral replication. Interferons increase expression of major histocompatibility complex (MHC) molecules. Increased MHC I expression up-regulates viral
presentation to cytotoxic T cells. Stimulation of MHC II expression potentiates helper T cell response and subsequent release of cytokines that increase activity of other immune cells.\textsuperscript{67}

Viral cellular invasion activated type 1 interferons, which secrete fibroblasts and monocytes with interferon-specific receptors. Subsequently, this activates the classical Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway. The downstream result is an expression of proteins that inhibit viral replication.\textsuperscript{67} The role of interferon in SARS-CoV-2 is intriguing but duplicitous. The SARS-CoV-2 virus enters the cell following binding of a spike protein domain with the ACE2 receptor, which is upregulated by interferons and has previously been suggested to help lung cells tolerate damage. However, in the case of SARS-CoV-2, the up-regulation of ACE2 may actually exacerbate the disease. It is unclear if SARS-CoV-2 is utilizing the important role of interferon in our innate clinical immunity or if the beneficial effects of interferon outweigh the increased cellular entry it allows.\textsuperscript{68}

Interferons have been previously investigated for use against SARS-CoV. An in-vitro study of cell lines from patients infected with SARS-CoV showed that interferon alpha, beta, and gamma all inhibited SARS-CoV replication; however, interferon beta was five to ten times more effective and showed both prophylactic protection as well as antiviral potential after infection.\textsuperscript{69} Others suggest that type 3 interferons—specifically interferon lambda—could be a better therapeutic option in respiratory infections. Sun, et al. showed that interferon lambda was superior to type 1 interferons due to their specificity in the respiratory tract, thereby decreasing systemic side effects specifically an inflammatory response that is sometimes characterized by type 1 interferons.\textsuperscript{70}
Intranasal Antiviral Agents and COVID-19

Aerosolized interferon treatment has been shown to be effective in viral-mediated respiratory disease. Type 1 interferons have been shown to induce undesirable systemic side effects, such as fatigue, headache, pyrexia, myalgia, rigors, and psychiatric symptoms. However, topical formulations of recombinant human interferon alpha-2b have been shown to have no significant side systemic side effects. This formulation was used as a topical nasal spray in a placebo-controlled trial in children with hand, foot, and mouth disease. The children treated with the topical nasal interferon alpha-2b had a shorter duration of fever, oral ulcers, skin rash, and decreased appetite when compared to the placebo group. A new formulation of type 1 interferon – interferon beta-1a – was used in a double blind, placebo-controlled trial of asthma patients in attempts to decrease viral respiratory infections and thus asthma exacerbations (NCT 01126177). The proprietary interferon beta-1a formulation is the only aqueous preparation and is pH balanced to the respiratory mucosa making it an ideal therapeutic for inhalation. Although this study failed to meet its primary end point of better asthma control, it did show good evidence of enhanced innate immunity with increased production of antiviral genes in induced sputum.

Topical interferon is an intriguing target for SARS-CoV-2 therapy. Preliminary results of its use as a prophylactic for healthcare workers in Hubei, China shows no infections in the 2944 healthcare workers using the medication as a nasal drop. While well conducted, prospective trials are certainly needed in peer reviewed literature, this therapy offers immense promise as a well-tolerated, easy to deliver topical prophylactic against SARS-CoV-2 infection.

**Enhancing Mucosal Absorption Efficiency**

The advantages in nasal mucosa as a drug delivery medium include increased absorption rate, possible increased bioavailability through avoidance of hepatic first pass metabolism, and a less acidic pH environment. However, challenges include a poor retention time on membrane,
narrow absorption value, degradation via mucolytic enzymes, and a continuous mucociliary movement leading to washout.\textsuperscript{74}

\textit{Chitosan}

Chitosan is a cationic polysaccharide widely studied for its mucoadhesive enhancing properties in medication delivery. Chitosan can contain a wide array of chemically altered functional groups to enhance mucoadhesive properties and permeation effects via opening of epithelial tight junctions, and several studies have demonstrated superiority in chitosan bound medications compared to unbound forms. Currently, chitosan has FDA-approved uses as a wound healing agent. However, limited study has been conducted on nasal chitosan-based antiviral medications. Given chitosan’s flexibility and study as a strong mucoadhesive with generally low toxicity, more research is needed into possible nasal chitosan-based antiviral medications.\textsuperscript{75}

\textit{Liposomes}

Lipophilic/liposomal formulations have aided drug delivery across lipid bilayer cell membranes. Many FDA-approved medications such as doxorubicin, amphotericin B and others have liposomal drug formulations. Several in vitro and in vivo animal studies have found liposomal formulations to improve drug bioavailability across the mucosal membrane barrier.\textsuperscript{80}. However, despite the significant quantity of research around both chitosan and liposomal nasal nanoparticle formulations, there remains no FDA approved products of chitosan and liposomal based nasal drug delivery systems and further research in humans is needed to support clinical safety and efficacy.\textsuperscript{76}
Poloxamers

Poloxamers are a class of hydrogels, which are water-soluble and nonionic copolymers with amphiphilic and surface-active properties. Increasing temperature of their aqueous solutions creates a sol-to-gel transition above a critical gelation temperature. Hydrogels are used to facilitate localized, sustained release of a drug, thereby lower drug dosage, limiting administration frequency, and avoiding adverse effects. Poloxamers are FDA-approved as non-toxic solubilizer, emulsifier, stabilizer, and can be administered through oral, parenteral, and topical routes.77

Route and Medium of Drug Delivery

Solution Sprays

Intranasal drug delivery has been used for allergic rhinitis, chronic rhinosinusitis, opioid overdose, and topical anesthesia/decongestion for many years and has been widely studied in the literature.78 Factors that make this delivery option favorable are the relative ease of use in a home environment and good patient tolerance. The risk of inducing viral shedding is unknown, as these sprays are aerosolized and could elicit sneeze or coughing. Most sprays generate an aerosol that deposits in the anterior nasal cavity, with mucociliary clearance further carrying medications deeper into the nasal cavity. Newer exhalation delivery nasal sprays have been shown to distribute further within the nasal cavity (Figure 4).79 Nasal nebulizers have also been employed in the treatment of chronic rhinosinusitis and nasal polyposis; however, distribution of medication is not significantly different than that of the exhalation delivery systems and has higher associated equipment cost. The mucous layer within the nose renews within 20 minutes and is discarded into the nasopharynx, thus the speed at which the medication dissolves within the mucous layer and penetrates mucosa is critical for drug efficacy. Computational fluid
dynamics could be utilized to determine appropriate particle size, spray velocity, and dosing to help guide effective therapies.

**Saline Rinses**

Like solution sprays, intranasal saline rinses are widely available, utilized with and without the addition of medications, and generally well-tolerated. Further investigation on the risk of viral shedding are needed. Advantages suggested over sprays include the removal of the mucous barrier with the rinse action, in order to provide maximum interface between the drug and the mucosa itself.\(^\text{80}\) However, formulations of medications must be water-soluble in order to administer in this method.

**Gel**

Intranasal nanogels have been utilized for drug delivery in Alzheimer’s disease, migraines, depression, and schizophrenia.\(^\text{81}\) This medium can be utilized for both hydrophilic and hydrophobic drugs, distinguishing it from the above mentioned intranasal sprays and rinses that typically require a suspension. Additionally, the increased viscosity of the gel formulation may increase the residence time of the drug on the nasal mucosa, therefore increasing drug absorption through the mucosa.\(^\text{82}\) Increasing the viscosity may, in turn, interfere with normal ciliary beating and cause untoward negative side effects. Challenges include maintaining stable formulations with consistent dosing while preserving an adequate shelf-life and designing an efficient delivery system to administer the gel within the nasal cavity. Wang et al also propose a hybrid of technologies via an in-situ gel-forming system, where a solution instilled intranasally undergoes phase transition to a viscoelastic gel have been formulated to offer. Advantages of this system include increased retention in the nasal cavity and increased permeability through the mucous membranes.
Foam/Packing

Intranasal foam and dissolvable packing have been utilized for many years by Otolaryngologists for treatment of epistaxis, chronic rhinosinusitis, and treatment of post-surgical sinus cavities. Applications for drug delivery for psychiatric conditions, such as bipolar disorder and schizophrenia, have also been studied. Examples of intranasal foams include chitosan, carboxymethylcellulose, hyaluronic acid, and synthetic polyurethane foam. Nanoparticles used as reservoirs for hydrophobic drugs can be compounded within these foams to provide increased mucoadhesive properties and enhanced absorption of medications. This method would likely be more challenging for patients to self-administer, as most Otolaryngologists employ its use by direct administration by a medical professional rather than by patients themselves. Additionally, these foams are traditionally applied under at least topical anesthesia, and may be less tolerated by eliciting more sneezing and irritation than sprays/rinses.

Dry powders

Most intranasal sprays on the market are liquid suspensions; however, recreational drugs have been used in powder form for many years. More recently, dry mist nasal sprays have been introduced, which dissolves the medication in hydrofluoralkane (HFA) propellant. Non-aqueous propellants such as propylene glycol, isopropyl alcohol, and PEG400 are known to cause local irritation with chronic use, thus careful attention to the choice of propellant and possible adverse reactions must be considered. Other challenges for utilization of powders includes ability to distribute within the nasal cavity, controlling the particle size, protecting viability of powder during storage from humidification, and maximizing absorption by the mucous membranes.79
Nasal ointments have been in use for control of folliculitis within the nasal vestibule as well as for prevention of epistaxis; however, more recently interest has increased in drug delivery via nasal ointments, such as for allergic rhinitis. Via intranasal swabs, these ointments are easily applied by patients to the anterior nasal vestibule, with mucociliary clearance carrying medications further within the nasal cavity. The higher viscosity ointments again result in lower tendency to spread and may increase retention time within the nasal cavity, and the lipophilic properties of the ointment may enhance absorption by the nasal mucosa. Disadvantages of ointments, specifically long-chain mineral hydrocarbons, include risk of paraffin granulomas and case reports of lipoid pneumonia from long-term nocturnal intranasal application.

**IMPLICATIONS FOR PRACTICE**

Topical intranasal antiviral drug delivery has several potential applications, but further studies are necessary. Efficacy in many settings is currently unknown, and considerations for any potential adverse effects, including loss of taste and smell, epistaxis, and mucosal irritation, are important.

The panel discussed the following settings in which studies of topical intranasal delivery of antiviral medications could be considered (Figure 5):
• Perioperative prevention for healthcare workers and patients

• Prevention of the well person from contracting the virus

• Prevention of the infected person or presymptomatic carriers from spreading the virus

• Systemic drug delivery

• Treatment of intranasal viral disease

• Reduction in progression of viral disease

Perioperative application as an antiseptic is the most mentioned use of intranasal (as well intraoral) antiviral agents. Several articles have described considerations of usage of povidone-iodine during oral and head and neck surgery, as well as in-office application for prevention of viral spread during minor endoscopic procedures, such as diagnostic nasal endoscopy and flexible fiberoptic nasolaryngoscopy. While clinical settings are the ideal initial areas for investigation, studies of community populations could be considered for the widespread prevention of spread and as potential therapeutic options for nasal symptomatology.

The nasal cavities and nasopharynx harbor a significant amount of SARS-CoV-2, even in asymptomatic or presymptomatic carriers of the virus. Several possible candidates exist for intranasal delivery of virucidal drugs and agents; however, clinical efficacy would require the agent(s) to have adequate mechanisms of target or viral cellular infiltration along with routes of delivery and medium suspension to reach the pathologic areas. Cellular absorption enhancement agents may also be needed to increase effectiveness. And as with any therapeutic agent, proper safety profiles for intranasal use are important. This article summarizes the current knowledge
from the literature regarding intranasal drug delivery and its potential applications in combating the SARS-CoV-2 pandemic and other future viral epidemics.
REFERENCES


Intranasal Antiviral Agents and COVID-19

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Table 1. Evidence for topical intranasal antiviral therapies. (+): yes, there is evidence. (-): no, there is evidence against statement; NS: not studied; adverse reactions tested: mucosal or skin irritation (I), smell and taste disturbance (ST), headaches (H), allergic reactions (A), nasal bleeding (B), fungal infection or colonization (F), and rhinosinusitis (RS); HFMD: Hand Foot Mouth Disease

<table>
<thead>
<tr>
<th>Agents (antiviral mechanism)</th>
<th>SARS-CoV-2</th>
<th>Other Viruses</th>
<th>Adverse Reactions</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In vitro activity</td>
<td>In vivo activity</td>
<td>Clinical efficacy</td>
<td>In vitro activity</td>
</tr>
<tr>
<td>Alcohol and Isopropanol (virucidal)</td>
<td>+</td>
<td>NS</td>
<td>NS</td>
<td>+</td>
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<tr>
<td>Hydrogen peroxide (virucidal)</td>
<td>+</td>
<td>NS</td>
<td>NS</td>
<td>+</td>
</tr>
<tr>
<td>Povidone-Iodine (virucidal)</td>
<td>+</td>
<td>NS</td>
<td>NS</td>
<td>+</td>
</tr>
<tr>
<td>Intranasal Antiviral Agents and COVID-19</td>
<td>smell/taste loss has not been evaluated.</td>
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<tr>
<td><strong>Carageenan</strong> <em>(prevents viral attachment)</em></td>
<td>Carageenan nasal sprays have shown efficacy in reducing viral loads and symptoms versus placebo in several RCTs. No nasal irritation were noted, but other adverse effects were not evaluated.</td>
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<tr>
<td><strong>Acid-Buffered Saline</strong> <em>(virucidal)</em></td>
<td>Acid-buffered saline nasal gels have been used in several studies demonstrating ability to reduce viral load and symptoms.</td>
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<tr>
<td><strong>Hypertonic Saline</strong> <em>(promotes innate antiviral immune response)</em></td>
<td>Hypertonic saline irrigation is well tolerated with minor discomfort in many other diseases and has been shown to reduce symptoms, viral shedding, and transmission of the common cold.</td>
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<tr>
<td><strong>Probiotics</strong> <em>(may promote innate immunity and antibody production)</em></td>
<td>Nasal probiotics have been shown to be well tolerated in CRS but have not been studied for antiviral purposes. Oral probiotics have shown efficacy in animal and human studies with common upper respiratory viruses.</td>
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<tr>
<td><strong>Surfactants/Shampoo</strong> <em>(prevents viral plasma membrane fusion)</em></td>
<td>Surfactant has been shown <em>in vitro</em> and <em>in vivo</em> (lungs) to have antiviral properties. Nasal surfactant or shampoo rinses are usually well tolerated but</td>
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</tbody>
</table>
Intranasal Antiviral Agents and COVID-19

have had reports of nasal irritation and reversible smell loss. Intranasal surfactant efficacy against viruses has not been studied.

| UV (virucidal) | + | NS | NS | + | NS | NS | NS: I, ST, H, A, B, F, RS | UV-C radiation is virucidal to SARS-CoV-2, but its use intranasally and its safety profile has not been studied. Far UV-C light may be less harmful but retain its antimicrobial properties. |
| Oxymetazoline and Xylometazoline (unknown) | NS | NS | NS | NS | + | + | Y: I NS: ST, H, A, B, F, RS | Small study shows that nasal decongestant may reduce viral shedding temporarily in rhinovirus. Extended use is known to cause mucosal irritation and rebound nasal congestion. |
| Interferon (multiple pathways) | NS | + | + | + | + | + | NS: ST, H, A, B, F, RS | Systemic interferon induces multiple side effects, but intranasal preparations have been shown to have antiviral properties and well tolerated. Topical nasal drops were used as prophylaxis in healthcare workers in Hubei, China during the beginning of the epidemic with no infections recorded in this population. |
FIGURE LEGENDS

Figure 1. Mind map graphically displaying the ideas and concepts of intranasal drug delivery in the setting of antiviral disease, including SARS-CoV-2. The central topic has branches extending in a radial fashion to connect subtopics. Each subtopic is connected to key concepts.

Figure 2. Structure of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Reprinted from Shereen, et al. 2020.8

Figure 3. The life cycle of SARS-CoV-2 in host cells. ACE2, angiotensin-converting enzyme 2; ER, endoplasmic reticulum; ERGIC, ER–Golgi intermediate compartment. Reprinted from Shereen, et al. 2020.8

Figure 4. Gamma camera image information from the nasal cavity superimposed on the corresponding sagittal MRI section presenting deposition two minutes after delivery using: (A) a traditional liquid spray, (B) the breath-powered powder device, and (C) the breath-powered liquid spray device incorporating the same spray pump. Reprinted from Djupesland, et al. 2012.79

Figure 5. Potential applications of intranasal drug delivery.
Figure 2

The mechanism of SARS-CoV-2 involves several key steps:

1. **Attachment and Entry**: SARS-CoV-2 binds to the ACE2 receptor on the host cell's surface.

2. **Fusion**: The viral spike protein fuses with the cell membrane, allowing the viral genome to enter the cell.

3. **Uncoating**: The genomic RNA is released from the viral capsid.

4. **Genomic RNA (Positive)**: The genomic RNA is translated into two replicase proteins, ORF1a and ORF1b.

5. **Replication/Translation**: The replicase proteins then replicate the genome and translate it into mRNA.

6. **mRNAs**: Multiple mRNAs are produced, each encoding different viral proteins.

7. **Translation**: The translated proteins include:
   - **Spike (S)**: Essential for viral entry.
   - **Envelope (E)**: Helps in virus assembly.
   - **Membrane (M)**: Forms the viral envelope.
   - **Nucleocapsid (N)**: Encapsulates the viral genome.

8. **Assembly and Budding**: The viral proteins are assembled into new virus particles in the endoplasmic reticulum (ER) and Golgi apparatus, which are then released from the cell via exocytosis.

The diagram illustrates the intricate process by which SARS-CoV-2 infects and replicates within a host cell.
Figure 3 - Mind Map - Intranasal COVID19.jpg
Potential Applications for Intranasal Drug Delivery

- Community Spread Prevention
- Healthcare Spread Prevention
- Systemic Drug Delivery
- Nasal Symptom Treatment