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A REVIEW ON UTILIZATION OF INTRANASAL ROUTE FOR THE EFFECTIVE ADMINISTRATION OF ANTIVIRAL DRUGS IN THE TIME OF COVID – 19 PANDEMIC

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ABSTRACT

The outbreak of SARS Corona virus has affected a huge population across the globe specifically people with weak immunity. The global pandemic of COVID – 19 has surpassed all previous pandemics in terms total contaminated population and the mortality rate. This review article discusses the current status of intranasal drug delivery systems being used for the administration of various antiviral drugs. Further it includes advantages and disadvantages of drug delivery system with emphasis of future applications to manage COVID – 19 and similar situations.

Keywords: Corona pandemic, COVID – 19, Intranasal drug delivery systems, Antiviral drugs

INTRODUCTION

Two main ways of SARS –COV-2 spread has been identified as airborne droplets and transmission with contaminated fomites. This virus can survive on solid surface for several days, however being an enveloped viruses it's possible to desiccate them using mild detergent disinfection. Reports suggest that cases of SARS-CoV-2 infections in the range of 6 to 88 % do not get converted in over disease. About 44% of individuals are infected by contracting virus from asymptomatic persons. Severity of symptoms differs from patient to patient. Elder Patients with weak immunity and others who are suffering from diabetes as well as cardiac and pulmonary conditions are reported to show highest fatality **[1]**.

SARS-COV-2 belongs to the group of enveloped positive sense RNA viruses. The genome length is reported to be

approximately 30,000 neucleotides encoding 16 non-structural proteins. However variation in the absolute numbers have been reported in other types of corona viruses. Coronavirus particles are reportedly spherical with the average diameter of 125 nm. The crown like appearance due to glycoprotein spikes are the reason for the nomenclature of genus. Apart from having spike glycoproteins, virus also have E and M integral membrane proteins, a host derived lipid envelope and the helical viral nucleocapsid comprising of the N protein and the viral genomic RNA **[2]**.

The first step in the beginning of the corona virus life cycle is the attachment of the viral particle to the host cell via the viral spike glycoprotein. The cellular receptors responsible for the viral entry varies among individuals. The entry of the viral RNA into the cytoplasm results in the expression of the viral replicase complex. This complex in made up of about 16 nonstructural proteins encoded by the genomic RNA. By a complex discontinuous RNA synthesis mechanism a nested set of mRNA transcripts are produced within the viral replication compartment. Further this produces complementary negative sense RNA templates. These nested mRNAs produce the viral structural proteins. The progeny viral genomes are produced by continuous viral RNA synthesis. The formation of new viral nucleocapsids takes place in the cytoplasm of the infected cell. The mature viral particles are grown into the endoplasmic reticulum-Golgi intermediate complex. The interaction between the endoplasmic reticulum-Golgi intermediate complex membrane associated M protein and N protein of the nucleocapsid facilitates the growth of viral particles. From here the mature viral particles are transported to the cell membrane in smooth walled vesicles and released to the extracellular space **[3, 4]**.

Up to this point, a total of 7 coronaviruses that are capable of infecting humans have been reported. Five to 10 percent of acute respiratory infections are triggered by these viruses. In most instances the corona virus allows upper respiratory infections to be self-limiting. However, SARS-COV-2 and MERS-COV have very high mortality rates relative to other forms of corona virus **[5]**.

The time of incubation ranges from around 7 days to 14 days. This varies on the degree of the person experiencing illness and symptoms. The high simple reproduction number of 2.5 to 3 is accounted for by this long asymptomatic process. In various anatomical sites, including nasal cavities, nasopharynx, sputum, oropharynx, bronchial fluid, and faeces, viral shedding has been recorded. Nasopharynx, however, has a far higher detection rate than oropharynx **[6]**.

A few agents have been reported to inactivate SARS-CoV-2 on the skin, including ultraviolet (UV) radiation, fire, alcohol, ethanol, and isopropanol, although no drugs have been developed specifically to control SARS-CoV-2. Various viruses were screened for other agents **[7]**.

1. Route and Medium of Drug Delivery

1.1 Solution Sprays

Intranasal drug delivery has been used for allergic rhinitis, chronic rhinosinusitis, opioid overdose, topical anaesthesia / decongestion for many years and has been reviewed extensively in the literature. The relative ease of use in home conditions and friendly user comfort are factors that affect this delivery option. As such sprays are aerosolized, the risk of causing viral shedding is not recognised and may cause sneezing or coughing. Some sprays create an aerosol of mucociliary clearance that is distributed in the anterior nasal cavity, taking drugs deeper into the nasal cavity. Newer exhalation nasal sprays have been seen to further disperse throughout the nasal cavity **[8, 9]**.

In the treatment of chronic rhinosinusitis and nasal polyposis, nasal nebulizers have also been used; however, drug administration does not differ significantly from that of delivery of exhalation products and has higher associated system costs. After 20 minutes, the mucous layer inside the nose renews and is recycled into the nasopharynx, so the rate at which the drug dissolves inside the mucous layer and penetrates the mucous membrane is important for the efficacy of the drug. Computational fluid dynamics may be used to assess the required particle size, spray velocity, and dosing to help direct successful therapies **[10]**.

1.2 Saline Rinses

Intranasal saline rinses are widely available, used, and generally well accepted, with and without the application of drugs, much like solution sprays. The probability of viral shedding needs further analysis. In order to have optimal contact with the liquid and the mucosa itself, the advantages provided over sprays include removing the mucous membrane via the rinsing process. In addition, to be administered using this method, pharmaceutical products need to be water-soluble **[11]**.

1.3 Gel

Intranasal nanogels are used for drug delivery for Alzheimer's disease, migraines, anxiety, and schizophrenia. This medium will be used to distinguish it from the above intranasal sprays with hydrophilic and hydrophobic substances which typically require suspension. In addition, increased gel formulation viscosity will increase the length of the drug's residence on the nasal mucosa, thereby increasing drug absorption

through the mucosa. Increasing the viscosity can interfere with normal ciliary beating in turn and cause untoward negative side effects. The challenges include ensuring safe formulations with sufficient dosing while maintaining an appropriate shelf life and establishing an efficient system of delivery to deliver the gel into the nasal cavity. A technical model with an in situ fluid-forming approach was also proposed by scientists, where the intranasally instilled solution undergoes a phase transformation to a viscoelastic material. This system has the advantages of improved nasal cavity stability and increased mucous membrane permeability **[12, 13]**.

1.4 Foam/Packing

Intranasal foam and dissolvable packaging have been used by otolaryngologists for many years to treat epistaxis, chronic rhinosinusitis, and postsurgical sinus cavities. Drug delivery mechanisms, such as bipolar disorder and schizophrenia, have also been examined for psychiatric conditions. These include chitosan, hyaluronic acid, carboxymethylcellulose and synthetic polyurethane foam. Nanoparticles used as reservoirs for hydrophobic drugs may be compounded within these foams to provide enhanced mucoadhesive properties and improved absorption of drugs. It is possibly more difficult for patients to self-administer this treatment since most otolaryngologists use it by direct administration by medical practitioners rather than by patients themselves. Furthermore, these foams are typically applied under at least topical anaesthesia and can be less tolerated by causing further sneezing and discomfort than sprays / rinses **[14]**.

1.5 Dry Powders

The majority of intranasal sprays on the market are liquid suspensions, but recreational products have been used in powder form for many years. Most recently, nasal dry mist sprays that dissolve the drug in the propellant hydrofluoroalkane have been released. It is understood that nonaqueous propellants such as propylene glycol, isopropyl alcohol and PEG400 cause persistent local irritation, so particular attention must be paid to the selection of the propellant. The ability to spread in the nasal cavity, control particle size, protect the effectiveness of the material from moisture during storage and maximise the absorption of the mucous membrane are some obstacles to the application of powders **[15]**.

1.6 Ointment

Nasal ointments were used to manage folliculitis in the nasal vestibule and to prevent epistaxis, but more recently, interest in drug delivery via nasal ointments, such as allergic rhinitis, has increased. Via intranasal swabs, such

ointments are rapidly applied by patients to the anterior nasal vestibule, with mucociliary clearance taking medication deeper into the nasal cavity. Higher viscosity ointments frequently result in a reduced tendency to scatter, which may increase the time within the nasal cavity for keeping. The lipophilic properties of the ointment would also promote absorption by the nasal mucosa. The lipophilic properties of the ointment would also promote absorption by the nasal mucosa. The drawbacks of ointments, specifically long-chain mineral hydrocarbons, include the possibility of paraffin granulomas and case reports of long-term nocturnal application of intranasal lipoid pneumonia **[16]**.

Table: 1 summary of available antiviral agents with the status of their in vivo and in vitro studies [17-25]

Antiviral Agents	In vitro activity	In vivo activity	Summary
Alcohol and isopropanol	Yes	Not studied	Surface preparations for alcohol and isopropanol have rapid virucidal effects on SARS-CoV-2 and other viruses although they can induce nasal inflammation. The application of intranasal swab has shown antibacterial effects without nasal inflammation.
Hydrogen peroxide	Yes	Not studied	H_2O_2 was used for several years as a disinfectant and does SARS-CoV-2 and other viruses have effectiveness Vitro. In vitro. Profile of intranasal protection is uncertain.
Povidone-iodine	Yes	Not studied	Anterior versions of the nasal versions are generally accepted. In vitro preparations have shown SARS-CoV-2 and other viruses to have severe virucidal impacts. Profile of detrimental consequences on humans is incomplete. Povidoneiodine may have ciliotoxic consequences, although no loss of smell / taste was detected.
Carrageenan	Not studied	Not studied	Carrageenan nasal sprays have shown efficacy in Viral loads and signs elimination or placebo Across a number of randomized experiments randomised. No nasal inflammation was observed but there was no assessment of any side effects.
Acid-buffered saline	Not studied	Not studied	Saline nasal gels with acid buffer is used in the Several reports suggesting decreased capacity Virus and signs.
Hypertonic saline	Not studied	Not studied	Hypertonic saline irrigation in many other diseases is well tolerated with mild irritation and has been shown to reduce the effects, virus shedding and general cold transmission.
Probiotics	Not studied	Not studied	Nasal probiotics in recurrent rhinosinusitis have been seen to be well tolerated, but were not tested for antiviral purposes. Oral probiotics shows an effectiveness with specific upper respiratory viruses in animal and human studies
Surfactants/shampoo	Not studied	Not studied	The surfactant has been demonstrated to have antiviral effects in vitro and in vivo (lungs). Nasal surfactant or shampoo rinses are usually well tolerated but have documented nasal pain and lack of reversible odour. There has been no analysis of the intranasal surfactant effectiveness against viruses.
UV	Yes	Not studied	UV-C radiation is virucidal to SARS-CoV-2, but its useintranasally and its safety profile have not been studied. Far UV-C light may be less harmful but retain its antimicrobial properties.
Oxymetazoline and xylometazoline	Not studied	Not studied	Relatively small study shows that in rhinovirus, nasal decongestant can temporarily reduce the viral shedding. Extended usage is known to cause inflammation to the mucosa and rebound nasal obstruction.
Interferon	Not studied	Yes	Systemic interferon causes many adverse effects although it has been demonstrated that intranasal formulations have antiviral properties and are well tolerated. In health care staff in Hubei, China, topical nasal drops were used as prophylaxis at the start of the outbreak with no infections reported in this community.

CONCLUSION

The most reported usage of intranasal (as well as intraoral) antiviral agents is perioperative use as an antiseptic. Many studies have identified implications of PI usage during oral and head and neck treatment, as well as in-office use for viral spread protection during minor endoscopic procedures, such as nasal endoscopy diagnosis and portable fiber optic nasolaryngoscopy. Although the appropriate initial fields for study are hospital environments, urban sample trials may be regarded for the broad avoidance of spread and as possible treatment solutions for nasal symptomatology.

The nasal cavities and nasopharynx contain significant quantities of SARS-CoV-2, also in virus asymptomatic or presymptomatic carriers. There are some potential candidates for the intranasal distribution of virucidal drugs and agents; furthermore, therapeutic efficacy will allow the agents to provide sufficient target or viral cell penetration pathways with delivery routes and medium suspension to enter the pathological areas. To improve performance, cellular absorption enhancing agents can also be needed. As for every therapeutic product it is essential to provide appropriate protection profiles for intranasal usage. This article reviews existing literature information about the distribution of intranasal drugs.

REFERENCES

[1] Chin AWH, Chu JTS, Perera MRA, *et al*. Stability of SARS CoV- 2 in different environmental conditions. Lancet. Published online April 2, 2020. doi:10.1016/S2666-5247 (20) 30003-3

[2] Arons MM, Hatfield KM, Reddy SC, *et al*. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. N Engl J Med. Published online April 24, 2020. doi:10.1056/NEJMoa2008457

[3] Lytras T, Dellis G, Flountzi A, *et al*. High prevalence of SARS-CoV-2 infection in repatriation flights to Greece from three European countries. J Travel Med. 2020; 27(3): taaa054.

[4] Nishiura H, Kobayashi T, Miyama T, *et al*. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). Int J Infect Dis. 2020; 94: 154-155.

[5] He X, Lau EHY, Wu P, *et al*. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med. 2020; 26(5): 672-675.

[6] Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, Evaluation and Treatment

Coronavirus (COVID-19). Stat. Pearls; 2020.

[7] Fehr AR, Perlman S. Coronaviruses: An Overview of Their Replication and Pathogenesis. Springer; 2015.

[8] Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: origin, transmission, and characteristics of human corona viruses. J Adv Res. 2020; 24: 91-98.

[9] Shang J, Ye G, Shi K, *et al*. Structural basis of receptor recognition by SARS-CoV-2. Nature. 2020; 581(7807): 221-224.

[10] Chan JF-W, Kok K-H, Zhu Z, *et al*. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect. 2020; 9: 221-236.

[11] Loeffelholz MJ, Tang Y-W. Laboratory diagnosis of emerging human coronavirus infections—the state of the art. Emerg Microbes Infect. 2020; 9: 747-756.

[12] Wang W, Xu Y, Gao R, *et al*. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA. 2020; 323(18): 1843-1844.

[13] Pittet D, Allegranzi B, Boyce J. The World Health Organization guidelines on hand hygiene in health care and their consensus recommendations. Infect Control Hosp. Epidemiol. 2009; 30: 611-622.

[14] Rabenau HF, Kampf G, Cinatl J, Doerr HW. Efficacy of various disinfectants against SARS coronavirus. J Hosp Infect. 2005; 61: 107-111.

[15] Siddharta A, Pfaender S, Vielle NJ, *et al*. Virucidal activity of World Health Organization–recommended formulations against enveloped viruses, including Zika, Ebola, and emerging coronaviruses. J Infect Dis. 2017; 215: 902-906.

[16] Centers for Disease Control and Prevention. CDC statement for healthcare personnel on hand hygiene during the response to the international emergence of COVID-19. Published May 17, 2020. https://www.cdc.gov/coronavirus/2019-ncov/hcp/handhygiene. html

[17] Kratzel A, Todt D, V'kovski P, *et al*. Efficient inactivation of SARS-CoV-2 by WHO-recommended hand rub formulations and alcohols. Emerg Infect Dis. 2020; 26 (7). doi: 10.3201/eid2 607. 200915

[18] Steed LL, Costello J, Lohia S, Jones T, Spannhake EW, Nguyen S. Reduction of nasal *Staphylococcus aureus* carriage in health care professionals by treatment with a nonantibiotic, alcohol-based nasal antiseptic. Am J Infect Control. 2014; 42: 841-846.

[19] Eggers M. Infectious disease management and control with povidone iodine. Infect Dis Ther. 2019; 8: 581-593.

[20] Safety and efficacy information 3M kin and nasal antiseptic (povidone-iodine solution 5% q/q [0.5% available iodine] USP) patient preoperative skin preparation. Accessed April 24, 2020. https://multimedia.3m.com/mws/media/716788O/3m-skin-andnasal-antiseptic-safety-and-efficacy-brochure.pdf

[21] Rezapoor M, Nicholson T, Tabatabaee RM, Chen AF, Maltenfort MG, Parvizi J. Povidone-iodine-based solutions for decolonization of nasal *Staphylococcus aureus*: a randomized, prospective, placebo-controlled study. J Arthroplasty. 2017; 32: 2815-2819.

[22] Wada H, Nojima Y, Ogawa S, *et al*. Relationship between virucidal efficacy and freeiodine concentration of povidone-iodine in buffer solution. Biocontrol Sci. 2016; 21(1): 21-27.

[23] Kim JH, Rimmer J, Mrad N, Ahmadzada S, Harvey RJ. Betadine has a ciliotoxic effect on ciliated human respiratory cells. J Laryngol Otol. 2015; 129: S45-S50.

[24] Ramezanpour M, Smith JLP, Psaltis AJ, Wormald PJ, Vreugde S. In vitro safety evaluation of a povidone-iodine solution applied to human nasal epithelial cells. Int Forum Allergy Rhinol. Published online April 6, 2020. doi:10.1002/alr.22575

[25] Mady LJ, Kubik MW, Baddour K, Snyderman CH, Rowan NR. Consideration of povidone-iodine as a public health intervention for COVID-19: utilization as ‘‘personal protective equipment’’ for frontline providers exposed in high-risk head and neck and skull base oncology care. Oral Oncol. 2020; 105: 104724.