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Viewpoint

Proposed Intranasal Route for Drug Administration in the Management of Central Nervous System Manifestations of COVID-19

Ruqaiyyah Siddiqui and Naveed Ahmed Khan*

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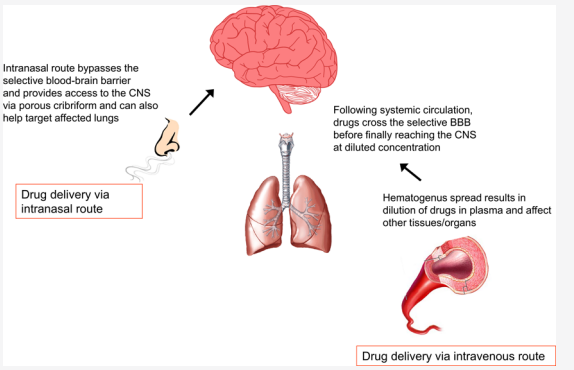
ABSTRACT: There is mounting evidence of the central nervous system manifestations associated with COVID-19, particularly in severe cases. Up to 25% of COVID-19 cases exhibit neurological manifestations associated with COVID-19. In view of the devastating nature of the disease due to severe acute respiratory syndrome coronavirus 2, here we debate intranasal drug delivery, in addition to intravenous delivery, as a therapeutic strategy in the management of COVID-19 cases with central nervous system involvement.



KEYWORDS: *COVID-19, severe acute respiratory syndrome coronavirus 2, central nervous system, neurological manifestation, intranasal*

Coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a serious respiratory illness. Recent reports suggest that, in severe cases of COVID-19, patients may have neurological manifestations, in addition to pulmonary damage.[1−3] In COVID-19 cases with the central nervous system involvement, as confirmed by brainstem concentration of infection, treatment involves intravenous injection of drugs.[4] Even with aggressive treatment, prognosis is often poor and attributed to (i) delayed diagnosis, (ii) inadequate comprehension of the pathophysiology and pathogenesis of the disease, (iii) lack of effective drugs available, and (iv) complexity in conveying anti-COVID-19 drugs to the infected brain. The intention of this Viewpoint is to deliberate if an enhanced therapeutic effect may be accomplished via the administration of drug therapy through the nasal cavity traversing the cribriform plate to access the brain, for COVID-19 cases with the central nervous system involvement.

Recent studies suggested two possible route of SARS-CoV-2 entry into the central nervous system.[5] It is well recognized that the route of viral entry into the central nervous system includes entry via the respiratory tract followed by virus invasion of the alveolar blood vessels, leading to hematogenous spread, while the entry into the central nervous system most likely occurs at the location of the blood-brain barrier, which is extremely selective in policing the entry of microbes and/or molecules. The olfactory neuroepithelium provides another route of entry into the central nervous system, bypassing the blood-brain barrier. Using the intranasal route, the drugs can reach the central nervous system via the porous cribriform plate as well as target the affected lungs. Clinical administration of drugs via the intravenous route results in dilution of the drugs in the plasma.[4] Moreover, even if drugs are injected into the cerebrospinal fluid, drainage into the venous blood via arachnoid villi is likely to reduce the concentration of the drug. In addition to the intravenous route, the use of intranasal route to administer drugs offers several advantages in the management of COVID-19 with neurological manifestations. The intranasal route can dispense the drugs through the cribriform plate. The cribriform plate is an anatomically porous bone, which is situated at the top of the nasal cavity. In this way, drugs can be given in a vaporized form to the inferior surface of the frontal lobe, before extending to the rest of the central nervous system to accomplish an effective concentration in the central nervous system. The proposed route is preferred as it will (a) circumvent the selectivity of the blood-brain barrier that restricts drug permeability to the brain tissue, (b) deliver

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drugs directly to the central nervous system, (c) exert effects of drugs at a lower dose without venous drainage, and (d) avoid adverse side effects due to systemic administration; (e) drugs can be given in the vaporized form to reach the porous cribriform plate. Furthermore, it is anticipated that intranasal delivery can offer admittance to the central nervous system without affecting the integrity of the blood-brain barrier. This proposed route renders obvious benefits over the conventional intravenous route, in that it will permit utilization of water-soluble drugs to attain an effective concentration of drugs at the epicenter of infection, overcome the blood-brain barrier impediment, and produce minimal adverse effects due to nonsystemic administration and dose adjustment at a quicker pace. This is further strengthened with the fact that many drugs do not attain an effective concentration in the brain/central nervous system through systemic administration. Additionally, the proposed delivery system will outweigh the current intrathecal and/or intraventricular routes that necessitate surgical procedures, thus having attendant complications. It is proposed that this route should be tested clinically in addition to the intravenous route. If efficacy of this route is proven, then it could either complement or replace the intravenous route for relieving neurological symptoms associated with COVID-19. Future research should test the efficacy of the suggested intranasal route for drug administration, in addition to the intravenous route, in the management of COVID-19 involving neurological manifestations.

AUTHOR INFORMATION

Corresponding Author

Naveed Ahmed Khan − *Department of Biology, Chemistry and Environmental Sciences, College of Arts and Sciences, American University of Sharjah, Sharjah, United Arab Emirates;* orcid.org/0000-0001-7667-8553; Phone: +971-6515-4752; Email: naveed5438@gmail.com

Author

Ruqaiyyah Siddiqui − *Department of Biology, Chemistry and Environmental Sciences, College of Arts and Sciences, American University of Sharjah, Sharjah, United Arab Emirates*

Complete contact information is available at: https://pubs.acs.org/10.1021/acschemneuro.0c00288

Author Contributions

Both N.A.K. and R.S. have a lifelong interest in the field of medical microbiology. All authors contributed equally to the manuscript and will act as guarantors.

Notes

The authors declare no competing financial interest.

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