

LETTER TO THE EDITOR

The potential of memantine and related adamantanes such as amantadine, to reduce the neurotoxic effects of COVID-19, including ARDS and to reduce viral replication through lysosomal effects

To The Editor,

I read the paper by Li et al¹ with interest regarding respiratory failure in coronavirus disease-2019 (COVID-19) associated with impaired spontaneous breathing likely being due to neurological impairment from central nervous system involvement. This may be from migration of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transynaptically from the lungs and nasal epithelium to the medullary cardiorespiratory center, via the peripheral nervous system from the lungs and through the cribriform plate from the nasal epithelium. Loss of sense of smell and taste is a common feature of COVID-19, and likely is associated with neurological involvement. The virus may be neurotrophic, the latent period from infection to development of complications being due to propagation of the virus from the lungs and nasal epithelium to the central nervous system.

Angiotensin-converting enzyme 2 (ACE2), the cell surface receptor for SARS-CoV-2 is located in the rostral ventrolateral medulla (RVLM), and attenuates "tonically active glutamatergic input" in hypertension.² Its depletion by SARS-CoV-2 would cause overactivity of angiotensin1-7 in the RVLM, activating the sympathetic nervous system, increasing blood pressure, causing systemic vasoconstriction, pulmonary capillary leakage, and acute respiratory distress syndrome (ARDS) from fluid in the alveoli.³

A study of the neurotrophic coronavirus OC43 with a single point mutation caused paralytic disease from glutamate excitotoxicity in susceptible mice, which was improved by memantine restoring a physiological neurofilament phosphorylation state.⁴ Memantine also reduced HCoV-OC43 replication in the CNS indicating it could be utilized as an antiviral agent and improve neurological diseases.⁴

Memantine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, to reduce glutamate toxicity through reducing prolonged Ca²⁺ influx in neurons, is used in treatment of Alzheimer's disease.

Besides coronavirus OC43, memantine has also been investigated with reference to other neurotrophic viruses such as rabies and Japanese encephalitis virus (JEV), and while of limited effectiveness in a rabies challenge experiment, mildly extending survival time in mice, in JEV, survival time was significantly increased, inflammatory cell infiltrates and intravascular cuffing were significantly reduced and mouse brain JEV content was less.⁵

Memantine was also able to prevent neuronal cell death in ZIKA virus through blocking NMDA receptors, although viral replication was unaffected.⁶

There were several patients with multiple sclerosis (n = 10), Parkinson's disease (n = 5), and cognitive impairment (n = 7), who were treated with adamantanes, 15 with amantadine, and seven with memantine, all the patients having SARS-CoV-2 documented by real-time polymerase chain reaction nasopharyngeal swabs, undergoing 2 week quarantine since documented exposure, and none developed clinical disease.⁷

Amantadine binds moderately with a pore formed by SARS-CoV protein E⁸ and downregulates the lysosomal enzymes, Cathepsin L /B (CTSL) genes, inhibiting their activity and raising lysosomal pH, which could interfere with the lysosomal phase of SARS-CoV-2 infection.⁹ Memantine is also a lysotropic agent,¹⁰ and could have similar effects to amantadine.

Memantine, may be a consideration as treatment for COVID-19, due to interfering with the NMDA activity, inhibiting excess glutamate release in the medullary brain stem, a potential neurotoxic effect from depleted ACE2, contributing to development of ARDS, and also inhibit viral replication through potential interaction with viral E protein (related adamantane-amantadine being studied in this regard), and lysosomal function.¹⁰

Memantine, amantadine and related adamantanes penetrate the blood-brain barrier. This is an advantage, although also a cause of potential side effects such as depression and confusion.


Side effects of memantine may include constipation, headache, and hypertension as well as slow or fast heart beat, bloating and swelling of the face, arms and hands as well as feet and legs.

Amantadine may cause bladder pain, confusion and swelling in the hands and feet, and inability to move the eyes. It does have effects on the nervous system and is utilized to treat levodopa-induced dyskinesia in Parkinson's disease.

Side effects of these medicines may overlap with symptoms of COVID-19, since as the pandemic progresses, more patients are being seen with neurological abnormalities, such as confusion, strokes, and seizures, which would require more detailed evaluation to determine the origin of such symptoms.

CONFLICT OF INTEREST

The author declare that there is no conflict of interest.

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