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Journal of Pharmaceutics & Pharmacology

Special Issue

Repurposing of Adamantanes for the Potential Prevention or Treatment of COVID-19

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Avens Publishing Group
J Pharmaceu Pharmacol
October 2020 Vol.8, Issue:1

Open Access Research Article

Journal of
Pharmaceutics & Pharmacology

Potential for the Use of Adamantanes for the Prevention and Treatment of the Neurological Complications of COVID-19

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Submission: 22 August 2020
Accepted: 02 October 2020
Published: 12 October 2020

Keywords: COVID-19; SARS-CoV-2; Adamantanes; Amantadine; Memantine; Disorders of consciousness; Neurodegeneration; Viral replication; Host cell proteases; Case reports; Clinical trials

Abstract

Widespread damage to the central and peripheral nervous systems resulting from COVID-19 is becoming well established. Features include impairments of the level [somnolence, stupor, coma] and content [confusion, delirium] of consciousness, impaired senses of taste, smell and vision as well as skeletal muscle manifestations. The neuroinvasive nature of SARS-CoV-2 may contribute to the acute respiratory failure of COVID-19. SARS-CoV-1 virus was detected in the brain of infected patients along with neuronal necrosis and glial hyperplasia. In SARS-CoV-2, modifications of crucial cellular pathways [mitochondrial function, proteolysis, lipid metabolism] known to be implicated in cellular aging and in neurodegenerative diseases occur. Adamantanes, [amantadine and the structurally-related memantine] are employed for the treatment of disorders of consciousness while also manifesting effective antiviral properties. Clinical studies and Case Reports at this early stage of COVID-19 reveal evidence of a protective effect of amantadine in infected patients with benefit being ascribed to amantadine's effects on viral release into the host cell via mechanisms involving the E channel of the virus or by the agent's down-regulation of the host protease Cathepsin L in addition to disruption of the lysosomal pathway. Memantine has potent neuroprotective actions in both well-established neurodegenerative diseases as well as in viral disorders in which it prevents neuronal cell loss and concomitantly reduces viral replication in a dose-dependent manner. Controlled clinical trials for the assessment of efficacy of these adamantanes for the prevention and treatment of COVID-19 are now indicated.

Introduction

Reports of the involvement of the CNS in relation to COVID-19 continue to appear. In a review of 214 hospitalized patients from Wuhan, China RT-PCR -confirmed diagnosis of COVID-19, neurological symptoms occurred in 45.5% of those with severe infection. Symptoms are generally classified into three categories namely CNS manifestations [dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, seizure], PNS manifestations [impaired taste, smell or vision, nerve pain] and skeletal muscle manifestations (Table 1). Impaired consciousness consisted of two facets namely change of level of consciousness [somnolence, stupor, coma] and content of consciousness [confusion, delirium] (Table 1). Acute cerebrovascular included ischemic stroke and cerebral haemorrhage diagnosed by clinical symptoms and CT [1].

A subsequent retrospective study of 113 deceased patients from Wuhan with COVID-19 described disorders of consciousness ranging from somnolence to deep coma in one third of patients and MRI evidence of a case of acute haemorrhagic necrotizing encephalopathy was reported in an adult COVID-19 patient consisting of haemorrhagic rim enhancing lesions in bilateral thalami, medial temporal lobes and sub-insular regions [2,3], (Table 1).

A description of what is considered to be the first case of meningitis/encephalitis in COVID-19 has appeared and it has been suggested that the neuroinvasive potential of SARS-CoV-2 may contribute to the pathogenesis of the respiratory failure characteristic of COVID-19 [4,5].

Mechanisms involved in the pathogenesis of the CNS manifestations of COVID-19 have not been definitively established but the presence of pro-inflammatory biomarkers in these patients suggests that SARS-CoV-2 related inflammatory mechanisms such as a "cytokine storm" could be implicated [6].

Coronavirus-induced neurodegeneration

Human coronaviruses [HCoVs] have well established neuroinvasive and neurotropic properties. In an extensive search and characterization of HCoV mRNA's in human brain autopsy samples from patients with a range of neurological diseases, a significantly higher prevalence of the OC43 strain was noted in Multiple Sclerosis [MS] patients. Three of four patients with Parkinson's disease [PD] showed increases of the 229E strain [7]. A previous study revealed increases in Cerebrospinal Fluid [CSF] antibodies to coronaviruses where responses to OC43 were greater than to 229E in PD patients [8].

Information relating to the cellular pathology and pathophysiologic mechanisms implicated in the CNS consequences of coronaviruses is largely derived from the results of studies in experimental animal models. HCoV-OC43 can infect and may persist in human neural cell lines with neuroinflammatory and neurodegenerative consequences. The virus causes encephalitis in susceptible mice and a single-point mutation in the viral spike protein results in paralysis [9]. The neurotropic and neuroinvasive properties of HCoC-OC43 were further characterized using an experimental

ISSN: 2327-204X

Table 1: Neurological manifestations of COVID-19.

CNS symptoms	PNS symptoms	Muscle symptoms
Dizziness Headache Altered level of consciousness[somnolence,stupor,coma] Altered content of consciousness [confusion,delirium] Ataxia Seizure Oculomotor disturbances Hypoxic encephalopathy	Impaired vision Loss of sense of taste [hypogeusia] Loss of sense of smell [hyposmia] Nerve pain	Myalgia Dystonia Myoclonus

Table 2: Amantadine and memantineindications.

AMANTADINE - Indications	References
Parkinson's Disease: motorsymptoms	FDA aproval
Parkinson's Disease: L-Dopa-induced dyskinesias	FDA aproval
Disorders of conciousness post-traumatic brain injury	Giacino 2018 [12]
Anti-viral: coronaviruses	Under Investigation
Fatigue in Multiple Sclerosis	Yang TT 2017 [13]
Restless Legs Syndrome (RLS)	Evidente VG 2000 [14]
MEMANTINE - Indications	**References**
Treatment of moderate to severe Alzheimer dementia	FDA approval
Mild to moderate Alzheimer dementia	Bakchine S 2008 [15]
Mild to moderate vascular dementia	Olivares D 2012 [16]
Neuropsychiatric disorders; behavioral and psychological symptoms	Lu S 2018 [17]
Parkinson's Disease	Olivares D 2012 [16]

animal model whereby virus inoculation of 21-day postnatal C57BL/6 and BALB/c mice manifested a generalized infection of the entire CNS demonstrating neuroinvasiveness and neurovirulence targeting neurons that showed vacuolation and degeneration. Damage was judged to be the result of virus-mediated neuronal injury and it was suggested that the prominent spongiform-like degeneration was sufficient to trigger significant neuropathology in surviving animals [9].

The SARS CoV-1 virus has been detected in the brains of patients following the 2002-3 SARS epidemic accompanied by neuronal necrosis, edema and glial hyperplasia. Infection of humans by SARS-CoV-1 results in substantial morbidity and death primarily from respiratory failure but the brain may also be affected resulting in long-term neurological sequalae. The brain is also a major target for infection in mice transgenic for human ACE-2, the receptor for SARS-CoV-1 [10]. Infection of the brain is consistently observed following intranasal inoculation in transgenic animals with brain regions such as thalamus, cerebrum and brainstem being particularly heavily infected. Death of infected animals appeared to be the result of dysfunction or death of infected neurons especially those located in cardio-respiratory centres in the medulla.

Given the rising body of evidence of destructive functional and cellular CNS changes associated with the current COVID-19 pandemic, an important issue that has not been thoroughly addressed relates to the long-term consequences to the health and quality of life of survivors. To date, modifications of proteostasis, mitochondrial function, lipid metabolism and stress responses have been identified as crucial cellular pathways that are adversely affected by SARS-CoV-2 and these pathways have been identified as those reported in cellular aging and in neurodegenerative diseases such as PD [11].

Protective effects of adamantanes

Amantadine and its structurally-related derivative memantine are members of the adamantane family that are commonly-prescribed for the treatment of CNS disorders (Table 2). Both have the ability to cross the blood-brain barrier and both are potent non-competitive antagonists of the NMDA receptor. Additionally, they each possess a myriad of other properties and mechanisms of action related to

ISSN: 2327-204X

coronaviruses and their effects on the [12-17], (Table 2).

Amantadine

Amantadine is an effective treatment for the motor disturbances characteristic of PD and for the dyskinesias resulting from L-Dopa in PD patients where its use results in a restoration of dopaminergic transmission in basal ganglia by the re-establishment of the balance between incoming nigrostriatal dopaminergic afferents with those of striatal glutamatergic inputs from the cortico-spinal tract [18].

Amantadine has also been found to be effective for the treatment of disorders of cognition and of consciousness [DoC's] resulting from Traumatic Brain Injury [TBI] [19]. Again, the beneficial effects of amantadine were judged to be the result of the stimulation of the production of dopamine *via* dopa decarboxylase secondary to NMDA receptor antagonism [20]. However alternative mechanisms have been proposed. For example, there is evidence in support of the notion that amantadine protects dopaminergic neurons by reducing microglial activation while simultaneously stimulating the growth factor GNDF in astroglia [21]. Either way, the evidence for the efficacy of amantadine for the treatment of DoC's has resulted in the updating of American Academy of Neurology practice guidelines for those disorders [12].

Of direct pertinence to the situation in COVID-19, DoC's of varying degrees of severity have consistently been reported during both the Wuhan and European outbreaks of COVID-19 in severely-infected patients [1,2,6,22]. Recommendations for the prevention and treatment of DoC's in COVID-19 have not yet been published but, given the success of amantadine for treatment of DoC's related to TBI, perhaps amantadine could be considered. After all, given the extent of neural damage attributed to SARS-CoV-2, perhaps COVID-19 is, almost by definition, a traumatic brain injury.

Translational studies to the clinic related to the potential treatment of COVID-19 have not yet appeared in the form of controlled clinical trials. However, three case studies, although descriptive and uncontrolled, provide evidence of beneficial effects of amantadine for COVID-19. These cases consist of the following:

In a single case report, a 57-year-old man who tested positive for SARS-CoV-2 by RT-PCR has been prescribed amantadine [100 mg bid]. His asymptomatic wife [54 yrs] and daughter [33 yrs] who also tested positive were prescribed amantadine [100 mg bid for 14 days] as a preventive measure. The patient's clinical status improved and by day 6 he was able to breathe without oxygen supplementation and was released on day 14. Neither of his family members developed clinical symptoms of COVID-19 [23].

In a subsequent study, five PD patients, mean age 68+/- 15 yrs, tested positive for COVID-19 [by RT-PCR in upper and lower respiratory specimens]. Infection was the result of person-to-person contact with infected persons in all cases and all had received amantadine [100 mg qid] for treatment of their PD for 3 months prior to their exposure to the virus. This had been followed by a 2-week quarantine. None of the 5 patients developed clinical manifestations of COVID-19 and their PD symptoms remained unchanged [24]. The authors concluded that these observations may hold potential for amantadine to prevent COVID-19 in vulnerable patients.

Following up on the above report, a 75-year-old female patient with PD of 16 years duration treated with medications for the treatment of hyperthyroidism and stomach cancer in addition to L-Dopa for her PD also received amantadine [100 mg/d]. Sometime later, the patient's husband showed classic symptoms of COVID-19 and he tested positive by RT-PCR. Bilateral pneumonia occurred resulting in hospitalization and his death. 45 days later, the patient had still not shown any signs of COVID-19 [25]. The author went on to make a plea for further studies in PD patients on amantadine therapy who become infected with SARS-CoV-2 in order to further substantiate these findings.

Important advances have been made relating to the potential mode of action of amantadine against SARS-CoV-2. One hypothesis relates to the effect of amantadine which, upon entering the E channel of the coronavirus, prevents release of the viral nucleus into the host cell. Docking studies suggest an interaction of amantadine with the amino acids ALA 22 and PHE 26 thus blocking the proton channel [26]. An independent but contemporary investigation provides evidence for a down-regulatory effect of amantadine on expression of the host cell protease Cathepsin L in addition to disruption of the lysosomal pathway resulting in interference with the capacity of the SARS-CoV-2 virus to replicate [27].

Memantine

It is generally accepted that glutamate [NMDA] receptor-mediated excitotoxicity is implicated in the pathogenesis of neuronal cell death in a wide range of neurological and neurodegenerative human conditions including Huntington's disease, amyotropic lateral sclerosis and multiple sclerosis. Comparable excitotoxic mechanisms have also been proposed to explain the CNS consequences of viral infections [28]. Primary neurons cultured *in vitro* and infected with Rabies Virus [RABV] manifest severe neuronal damage that was prevented by the addition of memantine [29]. In the same study, memantine was found to extend the survival time of mice infected with Japanese encephalitis virus [JEV] while decreasing the amount of virus in the brain.

In studies of neuroinvasive human respiratory coronaviruses, a viral mutant of HCoV-OC43 with a single-point mutation in the viral surface spike protein resulted in a paralytic disease that implicated glutamate excitotoxicity [30]. Memantine treatment led to improvements in motor performance, body weight loss and mortality along with a reduction of viral replication in the CNS in a dose-dependent manner. The authors suggested that memantine could be useful as a prophylactic and therapeutic antiviral agent.

Case reports of clinical benefit of memantine for COVID-19 have started to appear in the literature. Seven patients with cognitive impairment tested positive for SARS-CoV-2 by RT-PCR in upper and lower respiratory specimens. Infection occurred following person-to-person contact with infected individuals. All patients had been receiving memantine [100 mg bid] for at least 3 months prior to exposure to the virus and all had been quarantined for two weeks since documented exposure. No patients went on to report any clinical manifestations of COVID-19 and there were no significant

ISSN: 2327-204X

changes in neurological status [24].

Conclusion

Significant damage to both central and peripheral nervous systems resulting from COVID-19 is now widely established. Consistent features include impairments of both the level and content of consciousness, loss of sense of taste and smell, visionary loss, motor incoordination and seizures. The neuroinvasive properties of SARS-CoV-2 may contribute to the acute respiratory failure characteristic of COVID-19 and modifications of mitochondrial function, proteolysis and lipid metabolism characteristic of neurodegenerative diseases have been shown to occur. Basic research in molecular virology has identified mechanisms whereby members of the adamantine family of agents such as amantadine and memantine have significant antiviral properties with the capacity to impair replication of the virus. In addition, their well-established neurobiological mechanisms such as NMDA receptor antagonist actions are effective for the treatment of motor dysfunction and disorders of consciousness associated with a range of conditions including PD, traumatic brain injury as well as in human coronaviral infections.

Clinical studies so far consist principally of Case Reports and results are generally supportive of beneficial actions of adamantanes for the prevention of COVID-19 in exposed individuals. In the case of amantadine, benefit has been ascribed to its effects on viral release into the host cell involving the E channel of the virus or, alternatively/additionally to down-regulation and inhibition of the host cell protease Cathepsin L and disruption of lysosomal pathways. Memantine, on the other hand, has been shown to prevent neuronal cell loss while concomitantly impairing viral replication in a dose-dependent manner. Adequately-powered and appropriately-controlled clinical trials for the assessment of the efficacy and safety of these and other adamantanes identified in the present document for the prevention and treatment of COVID-19 are now indicated.

References

1. Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 77: 683-690.
2. Chen T, Wu D, Chen H, Yan W, Yang D, et al. (2020) Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 368: m1091.
3. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, et al. (2020) COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: Imaging Features. Radiology 296: E119-E120.
4. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, et al. (2020) A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis 94: 55-58.
5. Li YC, Bai WZ, Hashikawa T (2020) The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol 92: 552-555.
6. Leonardi M, Padovani A, McArthur JC (2020) Neurological manifestations associated with COVID-19: a review and a call for action. J Neurol 267: 1573-1576.
7. Arbour N, Day R, Newcombe J, Talbot PJ (2000) Neuroinvasion by human respiratory coronaviruses. J Virol 74: 8913-8921.
8. Fazzini E, Fleming J, Fahn S (1992) Cerebrospinal fluid antibodies to coronavirus in patients with Parkinson's disease. Mov Disord 7: 153-158.
9. Jacomy H, Talbot PJ (2003) Vacuolating encephalitis in mice infected by human coronavirus OC43. Virology 315: 20-33.
10. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S (2008) Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J Virol 82: 7264-7275.
11. Lippi A, Domingues R, Setz C, Outeiro TF, Krisko A (2020) SARS-CoV-2: At the Crossroad Between Aging and Neurodegeneration. Mov Disord 35: 716-720.
12. Giacino JT, Katz DI, Schiff ND, Whyte J, Ashman EJ, et al. (2019) Practice guideline update recommendations summary: Disorders of consciousness: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. Neurology 91: 450-460.
13. Yang TT, Wang L, Deng XY, Yu G (2017) Pharmacological treatments for fatigue in patients with multiple sclerosis: A systematic review and meta-analysis. J Neurol Sci 380: 256-261.
14. Evidente VG, Adler CH, Caviness JN, Hentz JG, Gwinn-Hardy K (2000) Amantadine is beneficial in restless legs syndrome. Mov Disord 15: 324-327.
15. Bakchine S, Loft H (2008) Memantine treatment in patients with mild to moderate Alzheimer's disease: results of a randomised, double-blind, placebo-controlled 6-month study. J Alzheimers Dis 13: 97-107.
16. Olivares D, Deshpande VK, Shi Y, Lahiri DK, Greig NH, et al. (2012) N-methyl D-aspartate (NMDA) receptor antagonists and memantine treatment for Alzheimer's disease, vascular dementia and Parkinson's disease. Curr Alzheimer Res 9: 746-758.
17. Lu S, Nasrallah HA (2018) The use of memantine in neuropsychiatric disorders: An overview. Ann Clin Psychiatry 30: 234-248.
18. Butterworth RF (2020) Amantadine for the Treatment of Parkinson's Disease and its Associated Dyskinesias. J Parkinsons Dis Alzheimer Dis 7: 1-7.
19. Butterworth RF (2020) Amantadine for the Treatment of Traumatic Brain Injury and its Associated Cognitive and Neurobehavioral Complications. J Pharmacol Pharm Res 3: 1-5.
20. Deep P, Dagher A, Sadikot A, Gjedde A, Cumming P (1999) Stimulation of dopa decarboxylase activity in striatum of healthy human brain secondary to NMDA receptor antagonism with a low dose of amantadine. Synapse 34: 313-318.
21. Ossola B, Schendzielorz N, Chen SH, et al. (2011) Amantadine protects dopamine neurons by a dual action: reducing activation of microglia and inducing expression of GDNF in astroglia [corrected]. Neuropharmacology 61: 574-582.
22. Manji H, Carr AS, Brownlee WJ, Lunn MP (2020) Neurology in the time of COVID-19. J Neurol Neurosurg Psychiatry 91: 568-570.
23. Aranda-Abreu GE, Aranda-Martínez JD, Araújo R (2020) Use of amantadine in a patient with SARS-CoV-2. J Med Virol 10.1002/jmv.26179.
24. Rejdak K, Grieb P (2020) Adamantanes might be protective from COVID-19 in patients with neurological diseases: multiple sclerosis, parkinsonism and cognitive impairment. Mult Scler Relat Disord 42: 102163.
25. Cortés Borra A (2020) Does amantadine have a protective effect against COVID-19? NeurolNeurochir Pol 54: 284-285.
26. Araújo R, Aranda-Martínez JD, Aranda-Abreu GE (2020) Amantadine Treatment for People with COVID-19. Arch Med Res :S0188-4409(20)30917-6.
27. Smieszek SP, Przychodzen BP, Polymeropoulos MH (2020) Amantadine disrupts lysosomal gene expression: A hypothesis for COVID19 treatment. Int J Antimicrob Agents 55: 106004.
28. Darman J, Backovic S, Dike S, Maragakis NJ, Krishnan C, et al. (2004) Viral-induced spinal motor neuron death is non-cell-autonomous and involves glutamate excitotoxicity. J Neurosci 24: 7566-7575.

ISSN: 2327-204X

29. Sun L, Zhou M, Liu C, Tang Y, Xiao K, et al. (2019) Memantine can relieve the neuronal impairment caused by neurotropic virus infection. J Med Virol 91: 935-940.

30. Brison E, Jacomy H, Desforges M, Talbot PJ (2014) Novel treatment with neuroprotective and antiviral properties against a neuroinvasive human respiratory virus. J Virol 88: 1548-1563.

Acknowledgement

Research from the author's Unit including costs of publication of original articles and reviews was funded over the last two decades by The Canadian Institutes of Health Research (CIHR) and The Canadian Association for Study of The Liver (CASL).