Memantine for the Treatment of Alzheimer's Disease: Novel Mechanisms and Future Opportunities

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Abstract

Results of a systematic review with meta-analysis of 30 Randomized Controlled Trials (RCTs) confirm the efficacy and safety of memantine when used as monotherapy or in combination with cholinesterase inhibitors for the treatment of Alzheimer's Disease (AD) where both cognitive function and behavioural disturbance scores were significantly improved. Food and Drug Administration (FDA) approval was subsequently granted for the treatment of moderate-to-severe AD. Mechanisms responsible for these beneficial effects include memantine's property as a non-competitive, low affinity, open-channel blocker of the N-methyl-D-aspartate (NMDA) receptor and its associated ion channel. An alternative explanation has emerged based upon the discovery that astroglia and microglia play a key role in the pathogenesis of neurodegenerative diseases together with reports of memantine's ability to control microglial activation and its associated anti-inflammatory response occurring independent of NMDA receptors. Additionally, by virtue of its established antiviral properties, memantine has also been proposed for the treatment of a number of neurodegenerative disorders with associated viral etiology. Neurodegenerative diseases including AD are considered to be co-morbidities of concern during the Coronavirus Disease 2019 (COVID-19) pandemic. *In vitro* studies confirm a beneficial effect of memantine against the E protein of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and a cohort of patients with severe cognitive impairment treated long-term with memantine developed no signs of infectious disease following Polymerase Chain Reaction (PCR) confirmed infection with COVID-19 while memantine-related improvements in neurologic status were maintained.

Keywords: Alzheimer's disease • Memantine • NMDA antagonist • Microglia • Systematic review • Meta-analysis • Ion channels • Viruses • COVID-19 • Amyloid precursor protein

Introduction

Alzheimer's Disease [AD] is a neurodegenerative disorder associated with acquired and progressive memory deficits with a high prevalence increasing exponentially with age doubling every 5 years from 60 to 80 years of age so that, between the ages of 80 and 85, the prevalence has been estimated to be as high as 25-30% of the population of Europe in 1990 [1]. From a neurochemical standpoint, AD results from neuronal cell loss from the nucleus basalis of Meynert resulting in a cholinergic deficit. These results led to intense investigations and clinical trials aimed at restoring the deficit using a range of agents such as cholinesterase inhibitors. Although somewhat effective from a symptomatic cognitive standpoint, these studies provided little by way of evidence relating to their use for the prevention of the neuronal cell death characteristic of AD.

Memantine: Non-competitive NMDA Receptor Antagonist

Memantine [adamantan-1-amine] is a member of the adamantane family of agents. The adamantane molecule is composed of three condensed cyclohexane ring structures fused together in an armchair configuration with a functional group substituted at one of the four methyne positions that determines the specificity of each individual compound. The Chemical structure of memantine is shown in (Figure 1).

Neuronal cell death in AD results at least in part by a process known as excitotoxicity resulting from excessive exposure to the excitatory neurotransmitter glutamate and more specifically via overactivation of a subclass of its receptor, the N-Methyl-D-Aspartate [NMDA] receptor leading to excessive release of Calcium [Ca^{++}] via the receptor's dedicated ion channel. Memantine blocks the overactivation of excess NMDA receptors but does so without disrupting normal excitatory transmission. This is attributed to memantine's property as a non-competitive, low affinity, open-channel blocker of the receptor [2]. Clinical experience supports these claims and confirms that memantine is well tolerated. A subsequent study addressed the precise mechanisms of interaction of memantine with NMDA-gated channels using mutational analysis and identified both specific and secondary memantine blocking sites. Indeed, memantine reacts with its specific blocking site in the same way as intracellular rather than extracellular magnesium (Mg^{++}) and the N-site asparagine (N) in the N_2 region of the NR1 subunit is the dominant site for the non-competitive

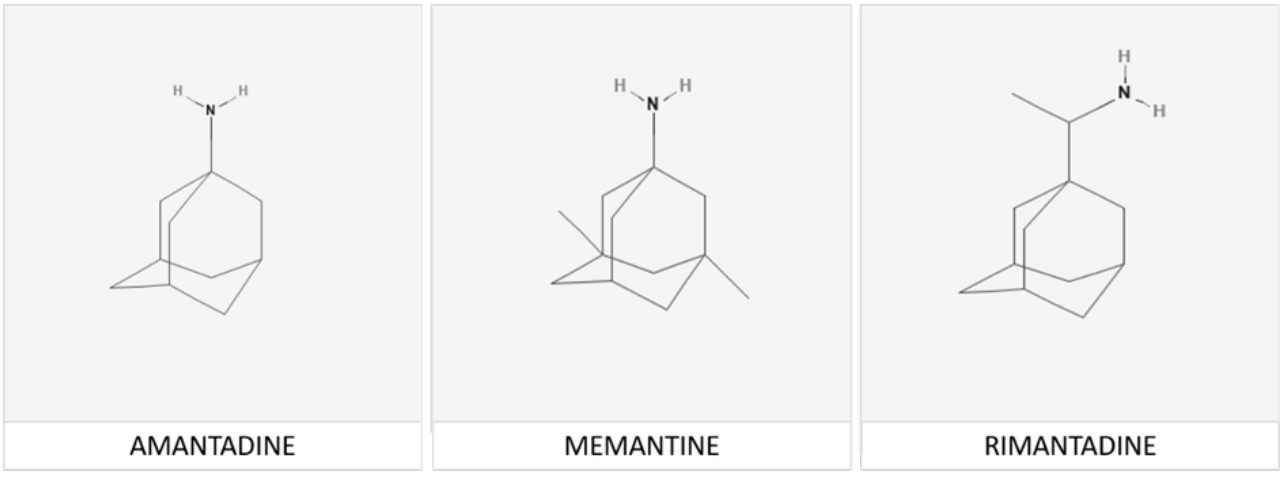

Figure 1. Chemical structures of memantine and its analogues rimantadine and amantadine.

antagonism by memantine [3].

Results of a systematic review with meta-analysis included results from thirty randomized placebo-controlled trials (RCTs) designed as follows:

Group 1: memantine vs placebo (11 trials, 3298 patients)

Group 2: memantine + a cholinesterase inhibitor (17 trials, 4175 patients) vs a cholinesterase inhibitor

Results indicated that memantine significantly improved both cognitive function scores with Standardized Mean Difference (SMD) -0.24, 95% CI: -0.34, -0.15, p=0.0001 and Behavioural Disturbances (BD) scores with SMD: 0.16, 95% CI: -0.29, -0.04, p=0.01 compared to placebo. In addition, memantine plus cholinesterase inhibitors produced a greater reduction of BD scores compared to cholinesterase alone with p=0.02. Sensitivity analysis in patients with moderate-severe AD, revealed that memantine was superior to placebo in reducing BD with p=0.003. On the basis of these and other findings, memantine was approved by the FDA for the treatment of moderate-to-severe AD either in the presence or absence of cholinesterase inhibitors [4].

Memantine: Anti-Inflammatory Effect Mediated by Attenuation of Microglial Activation

Memantine manifests anti-inflammatory properties in a wide range of disorders including hepatitis C and sepsis-induced neuroinflammation as well as in experimental models of multiple sclerosis and spinal cord injury [5]. Memantine has anti-inflammatory effects on human microvascular endothelium induced by Tumour Necrosis Factor Alpha (TNFα) in an experimental blood-brain barrier model where it prevents the attachment of monocyte THP-1 cells thus preventing the increase in expression of cell adhesion molecules [6]. In an associated dimension, diverse roles of glial cells (astroglia and microglia) continue to be reported in relation to neurodegeneration in general and to specific disorders such as AD in particular [7]. Microglial activation mediates an inflammatory response that contributes to the underpinning of mechanisms implicated in the pathogenesis of a range of neurodegenerative disorders including AD and Parkinson's disease [PD] [8] and a role for memantine in the control of microglial activation has been entertained with mechanisms entertained including increase in the release of Glial Cell Line Derived Neurotrophic Factor (GDNF) from astroglia through histone hyperacetylation of the GDNF promotor region via inhibition of cellular histone deacetylase and, secondly, via memantine's anti-inflammatory action by way of the inhibition of activation of microglia that is independent of NMDA receptors [9]. By way of an example, an illustration of the attenuation of Lipopolysaccharides (LPS) induced production of Reactive Oxygen Species (ROS) on the functional status of dopamine neurons treated with memantine in vitro is provided in (Figure 2).

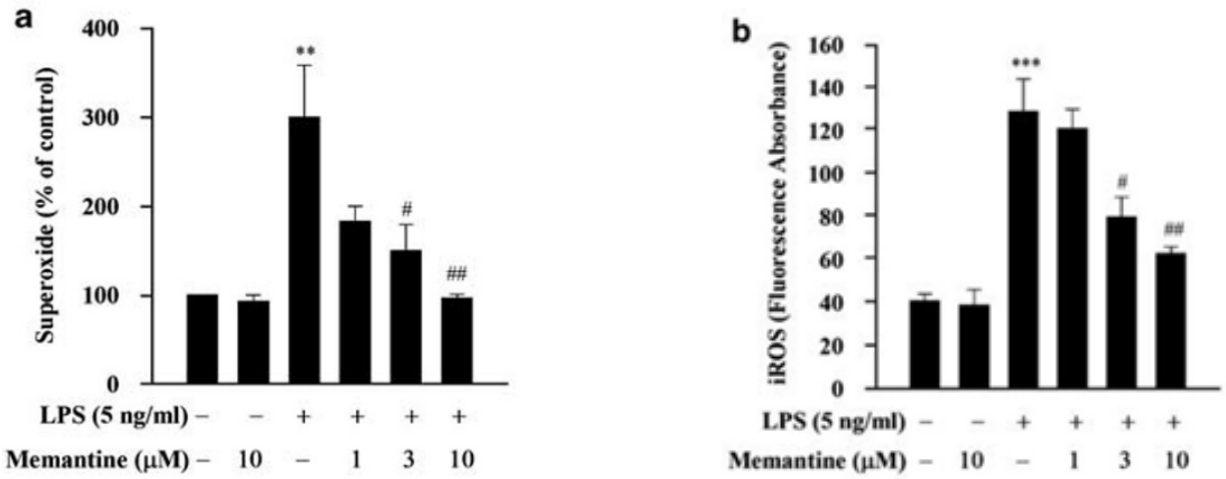

Figure 2. A: Attenuation of LPS-induced production of ROS and B: extracellular superoxide in microglial-enriched cultures pretreated with memantine (10 mM) for 30 min prior to LPS (5 ng/ml). Values expressed as mean +/- SEM of 3 independent experiments performed in triplicate **p<0.01 ***p<0.001 vs control by Bonferroni's T-test [9].

Memantine for Neurodegenerative Disorders Including AD

Related to Viral Infections

Memantine and other adamantanes are effective against a range of viral infections including those caused by neurotropic viruses such as the Rabies Virus (RABV) and Japanese Encephalitis Virus (JEV) both of which may result in neuronal dysfunction and pathological damage [10]. Moreover, in vitro experiments conducted in primary neurons infected with RABV showed evidence of neuroprotection when exposed to memantine and in a related series of experiments by the same authors, memantine was shown to decrease the amount of virus in JEV infected mice. An ongoing thesis proposes that Herpes Simplex Virus Type 1 (HSV-1) rather than p-tau is responsible for the inter-neuronal trans-synaptic pathological cascade proposed for the intracerebral propagation of AD that may reawaken interest in further studies of evidence in favour of a Herpes Simplex viral etiology for the disorder [11]. Whether or not the successful treatment of AD by memantine involves its antiviral action has not been established. Human coronaviruses also have neuro-invasive and neurotropic characteristics with the ability to activate mechanisms responsible for neuroinflammatory and neurodegenerative processes characteristic of AD and related neurological disorders. Such viruses activate neuroglial cells resulting in the production of proinflammatory mediators [12]. The Human Coronavirus (HCoV-OC43) is neuro-invasive in both humans and in mice. Moreover, memantine improved clinical scores and motor disabilities in mice infected by the virus while slowing body weight loss and decreasing mortality with concomitant reductions of viral replication all in a dose-dependent manner. These findings led investigators to propose that memantine be considered as an antiviral agent for the improvement of the neurological symptoms of neurological diseases of viral etiology [13]. Functional links continue to be identified between AD and COVID-19, the now infamous respiratory disorder caused by the coronavirus SARS-CoV-2. AD along with other neurodegenerative diseases is a common co-morbidity for COVID-19 and it has been proposed that the presence of the two conditions (AD or COVID-19) may result in worsening of the other [7]. The link is not surprising since both conditions are age related and both result in cognitive impairment and neurodegeneration. Both conditions are linked pathologically to Amyloid Precursor Protein (APP), NMDA-receptor activation and to microglial-mediated inflammatory responses as outlined in above sections. AD and COVID-19 share common pro-inflammatory signalling cascades so that, under certain conditions, AD-related neuroinflammation combined with that ascribed to SARS-CoV-2 have the potential to result in a "cytokine storm" resulting in poor clinical outcomes in both conditions. Amyloid-beta oligomers are known to transit into the plasma membrane forming pores that favour the passage of Ca ++ following activation of NMDA receptors and both AD and COVID derive therapeutic benefit from treatment with memantine. In relation to coronaviruses in general, memantine exerts dose-dependent neuroprotective and antiviral actions against the neuro-invasive human respiratory coronavirus HCoV-OC43 strain where the beneficial effects were ascribed to multiple factors including prevention of the release of proinflammatory cytokines due to reduction of microglial activation rather than to memantine's NMDA receptor antagonist actions. Studies in an experimental model of Chronic Obstructive Pulmonary Disease (COPD) reveal that memantine's beneficial effects were attributable to its anti-inflammatory actions related to its antagonist actions against a non-NMDA receptor known as the alph-7 subtype of the nicotinic cholinergic receptor [14]. From a mechanistic standpoint, results of

of *in vitro* studies of the SARS-CoV-2 virus itself reveal multiple possible mechanisms whereby memantine and the structurally-related amantadine manifest anti-coronaviral properties that include blocking of the viroporin channel of the E protein of SARS-CoV-2 thus preventing release of the viral nucleus into the host cell [15] Other proposed mechanisms include the downregulation in expression of host cell proteases such as Cathexin L [16]. The targeting of novel ion channels encoded by the virus has also been proposed [17].

Reports of efficacy of some adamantanes against SARS-CoV-2 have started to appear. In one such study, the efficacy of memantine, amantadine and rimantadine were evaluated for action against the virus; all are ion channel inhibitors and were tested against SARS-CoV-2 in Vero E6 cells *in vitro* shown in Figure 3 [18].

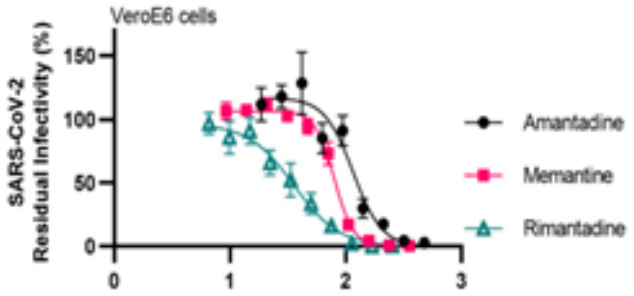

Figure 3. Potency of memantine compared to amantadine and rimantadine against SARS-CoV-2 in Vero E6 cells as a function of memantine concentration with SARS-CoV-2 infected cells visualized by immunostaining for spike protein [18].

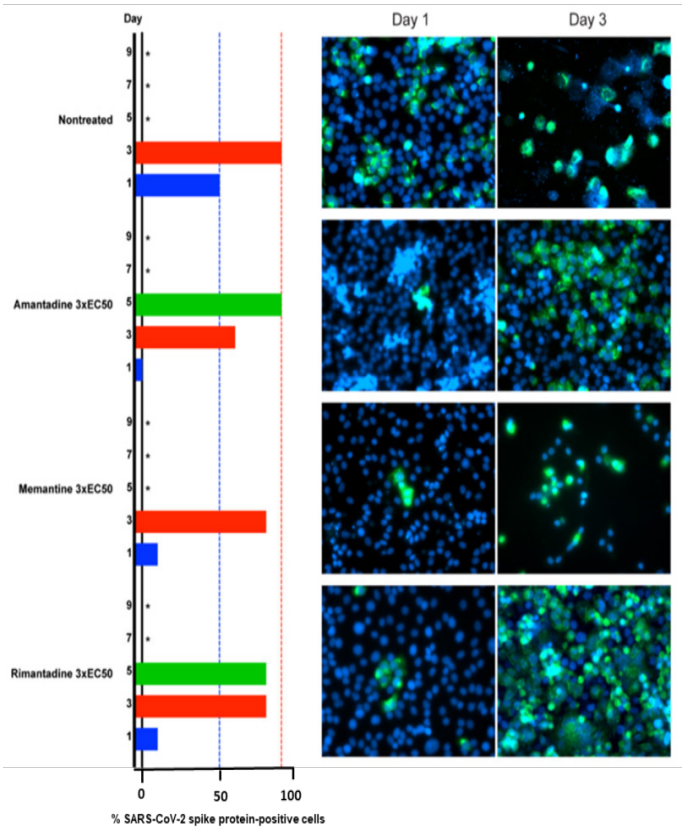

Figure 4. Barrier to SARS-CoV-2 escape by memantine and its analogues amantadine and rimantadine in their roles as ion channel inhibitors in Vero E6 cells at the concentrations of 3 x EC50 on days 1,3,5,7,9 post-infection. Infected cells were identified by immunostaining for SARS-CoV-2 spike protein (green) relative to counterstaining of cell nuclei with Hoechst dye (blue) [18].

All were effective including memantine but rimantadine was the most potent and showed highest selectivity index.

The barrier to SARS-CoV-2 caused by exposure to these ion channel inhibitors including memantine in Vero E6 cells at the concentrations of 3 x EC50 on days 1, 3, 5, 7, 9 post-infection are shown in (Figure 4).

Infected cells were identified by immunostaining for SARS-CoV-2 spike protein (green) relative to counterstaining of cell nuclei with Hoechst dye (blue) [18]. Clinical trials of the efficacy of memantine for the treatment of COVID-19 in patients with AD have yet to appear. However, a questionnaire-based study of 7 patients, mean age: 71±10yrs, mean disease duration: 7±2yrs [all tested positive for COVID-19 by Reverse Transcription-Polymerase Chain Reaction (RT-PCR)] had been receiving treatment with memantine (10 mg bid) for 3 months prior to infection. None of the treated patients went on to manifest clinical symptoms of infectious disease. These findings clearly warrant further investigation [19].

Summary and Conclusion

Results of the current review provide a summary of the current evidence in support of the claims of efficacy of memantine for the improvement of the cognitive dysfunction and behavioural disturbances characteristic of moderate-to-severe AD. The evidence base rests upon the examination and reviewing of the results of a number of RCTs of memantine versus either placebo or cholinesterase inhibitors. It was concluded that memantine treatment led to significant improvements of both cognitive function and behavioural disturbances. Moreover, the use of memantine plus cholinesterase inhibitors was determined to be significantly superior to the use of cholinesterase inhibitors alone. Largely due to the results of these trials, memantine gained approval from FDA (USA) for the treatment of moderate-to-severe AD either in the presence or absence of cholinesterase inhibitors.

Over the last two decades a number of mechanisms have been proposed to account for the beneficial effects of memantine for the treatment of AD and, by association, with other neurodegenerative disorders. Initially, it was proposed that memantine exerted its protective mechanism by virtue of its property as a non-competitive low affinity open channel blocker of the NMDA subclass of post-synaptic glutamate receptors leading to blockade of its dedicated Ca^{++} ion channel resulting in decreases of the process of excitotoxicity and consequently decreases of neuronal dysfunction and cell death. Some years later, increased attention has focused on the role of microglial cells in relation to neurodegenerative disorders including AD. Memantine is an established anti-inflammatory agent acting independent of the NMDA receptor. Rather, memantine acts by attenuation of the process of microglial activation. Thirdly there remains a robust interest in memantine by virtue of the molecule's antiviral properties against a range of neurotropic viruses including human coronaviruses and there remains a certain interest in the notion that HSV-1 may be implicated in the inter-neuronal trans-synaptic pathological cascade proposed for the inter-cerebral propagation in AD. AD shares common proinflammatory signalling cascades with COVID-19, the now infamous respiratory disorder for which the causal agent is the virus (SARS-CoV-2). It has been suggested that memantine's antiviral properties result from via an action involving blocking of the viroporin channel of the E protein of the virus or by down- regulation of expression of host cell proteases such as Cathexin L. Alternatively, the targeting of known or novel ion channels has been proposed. The extent to which such mechanisms are implicated in the pathogenesis of AD or other neurodegenerative diseases remains to be established.

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