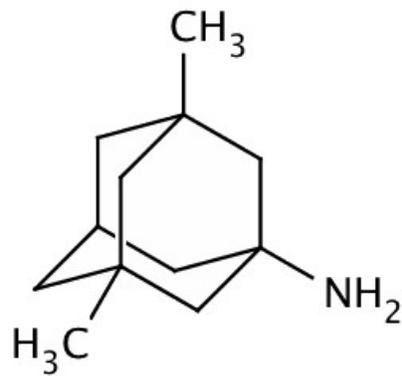


CINAPS COMPOUND DOSSIER

MEMANTINE



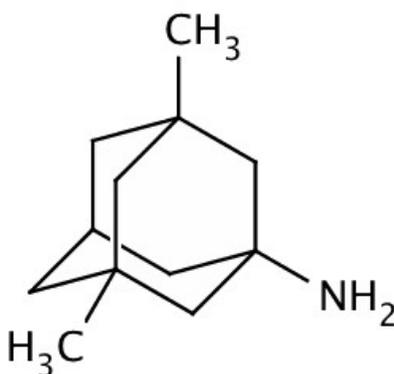
11/24/2009

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I. Compound Information

Common name: Memantine



Structure:

Pubchem ID: 4504 **Mol. formula:** C₁₂H₂₁N **FW:** 179.3

CASRN: 19982-08-2 **Polar surface area:** 26 **logP:** 3.3

IUPAC name: 3,5-Dimethyladamantan-1-amine

Other names: Namenda®

Drug class: NMDA receptor antagonist

Medicinal chemistry development potential: High

II. Rationale

Ila. Scientific Rationale / Mechanism

Voltage-dependent blockade of N-methyl-D-aspartate (NMDA) receptor: The principle biochemical/neurochemical basis for the therapeutic actions of memantine (MEM) involves uncompetitive blockade of the ion channels of the NMDA subtype of glutamate receptors. MEM has a favorable balance of rapid blocking/unblocking kinetics that is voltage-dependent, as comprehensively reviewed,^{1, 2} and this property is key to its efficacy and low side effects compared to other NMDA antagonists.

Under resting conditions (-70 mV) both MEM and Mg⁺² occupy the receptor channel. Both leave the channel under the strong synaptic depolarization (-20 mV) of normal physiological functioning, allowing influx of Ca⁺² ions. However, MEM contrasts with Mg⁺² in that it does not leave the channel so easily upon moderate prolonged depolarization (-50 mV) during chronic excitotoxic insults³ such as those mediated by glutamate. MEM is aptly described as a “better magnesium”,⁴ preventing the pathology of prolonged depolarization, yet displaceable as needed for normal functioning. Less favorable dissociation kinetics are implicated in the poorer tolerability of other adamantanes and NMDA antagonists. Alternate hypotheses of the blocking/unblocking action of MEM note the presence of channels that release MEM upon agonist removal (15-20% of channels), and differential NMDA receptor subtype selectivity to MEM.¹

Neuroprotection: MEM can achieve neuroprotection by modulating overactivity of NMDA receptors. Overactivity of NMDA receptors generates reactive oxygen species (ROS) and excessive nitric oxide (NO), and this can mediate protein mis-folding and other processes leading to neurodegeneration. Excessive activation of NMDA receptors drives Ca⁺² influx, which in turn activates neuronal NO synthase and generates ROS.⁵ ROS destroy Ca⁺² –ATPase, and hence the ability to expel Ca⁺² ions, exacerbating that effect. NO contributes to protein mis-folding *via* S-nitrosylation of protein-disulfide isomerase and also the E3 ubiquitin ligase parkin. Modulation of channels secondary to these oxidative events occurs through S-nitrosylation of sulfhydryls on the NMDA receptor, leading to disulfide formation and reduction of the activity of those receptor channels. The ubiquitin-proteasome system is important in protection against progression of PD by working with chaperones to remove abnormal proteins, such as those from α -synuclein; dysfunction of this system leads to accumulation of mis-folded aggregates. MEM was effective in protecting against amyloid aggregates.²

Glial cell line-derived neurotrophic factor (GDNF) supports neuritic outgrowth and survival of neuronal cells. Direct injection of GDNF into the cerebral ventricles, the striatum, or the sub-

stantia nigra of rodent and primate models of PD have proven effective in supporting fibers outgrowth and improvement of motor function. MEM induces the expression of GDNF in C6 glioma cells.⁶

MEM significantly attenuated malonate-induced striatal lesions, implying utility in chronic diseases associated with deficits in mitochondrial function.⁷

Preclinical Mechanistic Evidence of Neuroprotection and Caveats: After consideration of 47 literature citations, and the cautionary statements in the excellent reviews by Parsons *et al.*¹ and Sonkusare *et al.*,² it is important to note that other potential protective mechanisms explored in animal models may not be relevant to dose levels used in the clinic that proved to be well-tolerated and efficacious (20 mg/kg commonly in animal models, 20 mg total daily dose in humans). The steady-state plasma levels associated with the common clinical dose of 20 mg/day are 70-150 ng/mL (about 0.5-1 μ M), but are “20-50% lower in the CSF” due to protein binding. Parsons *et al.* concluded that “NMDA blockade is the primary, if not only, mechanism” of clinical import.¹

However, MEM prevents hypoxia/ischemia/reperfusion related damage surgically induced in animal models. MEM (20 mg/kg) significantly reduces infarct size in rats when administered 5, 15 or 30 min prior to, or up to 2 h post induction.^{1, 8-10}

Single bolus doses of MEM (25, 50, and 75 mg/kg ip) to rats induced Hsp 70 in the posterior cingulate, retrosplenial cortex and dentate gyrus of rat brain, suggesting a protective role mediated by the heat shock protein and its co-chaperones that could attenuate the toxic effects of abnormal proteins.¹ However, this has not been reproduced in primates, and the effect in rats was in response to relatively high doses of MEM.

Memory and Learning: As noted in a review by Parsons *et al.*¹, the main effect of MEM assessed in clinical trials so far has been symptomological improvement. Long-term potentiation (LTP), the long lasting enhancement of post-synaptic potential in response to a brief stimulus of high frequency, is responsible for long-term memory and changes in synaptic structure and strength in the hippocampus. Glutamate is the most important neurotransmitter involved in expression of LTP, and NMDA receptors are the most important mediator of that response. During learning and memory processes (high transient glutamate release), MEM can leave the NMDA receptor briefly so that a signal is produced that can be recognized and processed.² While LTP can be attenuated by NMDA receptor antagonists, MEM itself has minimal effect on LTP. Parsons *et al.*¹ advance the concept that tonic activation of NMDA receptors, in contrast to that for learning, produces synaptic ‘noise’ and leads to a loss of association detection; MEM attenuates the disruption of neuronal plasticity so induced by this stress. In studies in aged rats, MEM pro-

longed the duration of LTP in vivo and also showed a trend to improve memory retention in the Morris maze.⁸

Brain-derived neurotrophic factor (BDNF) enhances hippocampal synaptic transmission by increasing NMDA receptor activity. MEM also increases the levels of BDNF mRNA in the limbic cortex and induces isoforms of the BDNF receptor trkB.² Together these may be important mediators of the neuroprotective and memory-enhancing action of MEM.

Combination Therapy with L-DOPA: In the initial stages of PD, L-DOPA is effective in treating motor symptoms, but long-term treatment with L-DOPA has its drawbacks and is accompanied by many side effects, including motor fluctuations and dyskinesias. In mice and rats pretreated with MPTP, MEM was found to be a “synergistic and restorative” agent in combination with L-DOPA in combating the “wearing off effect” that occurs with the latter.^{11, 12}

Other mechanisms Considered: Additional mechanisms considered involved receptors other than NMDA receptors. MEM is a noncompetitive, voltage-dependent inhibitor (IC₅₀ of 2 μM) of 5-HT₃ receptor currents, and blocks the human nicotinic receptor at higher (6.6 μM IC₅₀) concentrations;² it was postulated that this may be the cause of MEM-induced depression in some patients. Drever *et al.*¹³ noted that stimulation, by MEM, of cholinergic signaling *via* muscarinic receptors likely contributes to its therapeutic action. However, these effects were found using 10 and 100 μM MEM, concentrations higher than those achievable in well-tolerated clinical regimens.

Parsons *et al.*¹, compared the activities of various receptors at relevant therapeutic concentrations of MEM. While the therapeutic range of MEM aligned with the EC₅₀s of NMDA receptors, there was no relevant binding to nicotinic, dopaminergic or serotonin receptors or on dopamine release or uptake at those receptors.^{1, 14, 15} Further, the interaction with the NMDA receptor did not involve aspartate, glutamate, glycine, or sigma-1 binding sites.

IIb. Consistency

n/a

III. Efficacy (Animal Models of Parkinson's Disease)

IIIa. Animal Models: Rodent

MEM induces antiparkinsonian activity in hypokinesia caused by MPTP treatment in mice, abated the "wearing off" effect of L-DOPA,¹¹ and increased locomotion in monoamine-depleted rats when administered with L-DOPA.^{12, 16} MPTP-mediated oligokinesia and muscular rigidity induced in rats was prevented by treatment with MEM at doses of 5 mg/kg and higher.¹⁷ The akinetic effect induced by treatment with 6-hydroxydopamine was compensated for by treatment with 10 mg/kg MEM in rats.¹⁸

IIIb. Animal Models: Non-human Primates

n/a

IV. Efficacy (Clinical and Epidemiological Evidence)

IVa. Clinical Studies

Clinical studies specifically addressing the efficacy of MEM in treating Parkinson disease are limited, but are supplemented by the wealth of information regarding its use in treatment of moderate to severe AD. In these studies, the effect on the same behavior and motor parameters common to PD were measured in studies that supported FDA and European regulatory agencies in their approval of MEM for treatment of AD. Additionally, the usual recommended dose of about 20 mg per day was commonly used for both indications.

A double-blind cross over randomized study of MEM in 12 patients with PD that had motor fluctuations and drug-induced (L-DOPA) dyskinesias was reported by Merello *et al.*¹⁹ 10 mg was administered b.i.d. for 2 weeks. While UPDRS motor scores were improved, there was no effect on dyskinesias induced by L-DOPA. Another aminoadamantane, amatadine, and other PD drugs such as tamoxifen, safinamide and geldanamycin, have this beneficial action, and lack of this therapeutic effect may limit the utility of MEM during treatment throughout the progression of PD.

In an early study by Rabey *et al.*,²⁰ 14 parkinsonian patients with motor fluctuations that were taking L-DOPA were given 30 mg daily doses of MEM. After one month, 10 patients completed the study. In 5 of the patients, the main parkinsonian features (rigidity, bradykinesias, tremor, gait, postural reflexes) improved significantly.

IVb. Epidemiological Evidence

n/a

V. Relevance to Other Neurodegenerative Diseases

The literature reviewed indicated that, secondary to antagonism of the NMDA receptor, MEM may be a beneficial therapeutic for the treatment of symptoms presented by a number of neurological diseases in addition to Parkinson disease. These include AIDS related dementia, hepatic encephalopathy (hyperammonemia-induced), multiple sclerosis, tinnitus, tardive dyskinesia (due to long-term treatment with neuroleptics), chronic pain, drug addiction, epilepsy, spasticity, depression and anxiety, stroke, dementia and pendular nystagmus.¹ While clinical evidence supports the efficacy of MEM for the treatment of Parkinson disease, spasticity, and dementia, the evidence for potential use in the other indications is largely built on preclinical models in which the concentrations of MEM may be higher than are well tolerated by patients.¹

Numerous clinical studies with AD patients treated with MEM have demonstrated positive outcomes in cognitive, functional, behavioral (including aggressiveness and agitation), and global assessments in moderate to severe AD.^{2, 21-25} MEM was often coadministered with donepezil, but was effective also as a monotherapy.^{21, 26}

MEM was approved by the FDA in 2003 for the treatment of moderate to severe AD, and is also approved in the European Union for this indication and for treatment of dementia.^{2, 21} It is also effective in treatment of dyskinesias and spasticity. At a daily dose of 20 mg, MEM significantly improved symptoms of chorea in patients with Huntington's disease.²⁷ MEM proved effective in animal models of tonic, but not clonic seizures, though at high doses. While perhaps not appropriate for monotherapy in epilepsy, MEM may be a promising therapeutic as part of a combination therapy.¹

Spasticity: MEM (10-20 mg/kg) selectively reduced polysynaptic spinal reflexes (related to spasticity) in rats.²⁸⁻³⁰

Neuroprotection: MEM provides neuroprotection from glutamate-mediated pathogenesis mediated by inflammation in the nucleus basalis magnocellularis or by amyloid injection to the hippocampus⁴, and prevents hypoxia/ischemia/reperfusion related damage surgically induced in animal models. MEM (20 mg/kg) significantly reduces infarct size in rats when administered 5, 15 or 30 min prior to, or up to 2 h post induction.^{1, 8-10}

Long-term Potentiation and Memory: Long-term potentiation (LTP), the long lasting enhancement of post-synaptic potential in response to a brief stimulus of high frequency, is responsible for long-term memory and changes in synaptic structure and strength in the hippocampus. Glutamate is the most important neurotransmitter involved in expression of LTP, and NMDA receptors are the most important mediator of that response. During learning and memory pro-

cesses (high transient glutamate release), MEM can leave the NMDA receptor briefly so that a signal is produced that can be recognized and processed.² While LTP can be attenuated by some NMDA receptor antagonists, MEM has minimal effect in disrupting LTP. MEM improved memory and LTP in moderately-aged rats, as demonstrated in Morris maze experiments conducted by Barnes *et al.*³¹, and similarly in models of stroke wherein LTP and learning were preserved under conditions in which MEM attenuated neurological damage induced by surgical models of stroke.^{8, 32} Preservation of LTP in rats was demonstrated in vivo (passive avoidance tests) and in vitro (LTP in the CA1 region).⁴ At a dose of 2 mg/kg in mice, MEM reverses scopolamine-induced learning deficits in mice, indicating stimulating effects on cholinergic signaling *via* muscarinic receptors.¹³

Anti-convulsant Activity: MEM inhibits NMDA-induced convulsions in mice (ID₅₀ of 4.6 mg/kg i.p.) and in rats (ID₅₀ of 9.7 mg/kg). It was effective in blocking tonic, but not clonic, seizures in mice and rats ¹.

Neurotoxicity in HIV Infection: The HIV-1 proteins Tat and gp120, found in the brains of patients with HIV-1 encephalopathy, are implicated in the pathogenesis of dementia associated with HIV infection. MEM greatly lowers gp120-induced increases in intracellular calcium responsible for neuronal damage.³³

VI. Pharmacokinetics

Vla. General ADME

In a study by Almeida *et al.*,³⁴ a single oral dose of 20 mg MEM to healthy volunteers resulted in a C_{max} of 32 ± 7 ng/mL (ca. $0.15 \mu\text{M}$), and a T_{max} of 2.7 ± 1.6 h. Sonkusare *et al.*² reported a T_{max} of 3-8 h, claimed “100%” bioavailability and noted no reports of an effect of food, sex or age on absorption. There were no differences observed in plasma steady state concentrations between healthy subjects and those with dementia. Under typical therapeutic doses in human subjects, serum levels of MEM with daily doses of 20 mg range from 0.4 to $1.0 \mu\text{M}$.^{1, 2} Steady state concentrations of MEM reach $0.2 \mu\text{M}$ in the CSF of patients following doses of 20 mg/day for 11 days, and a CSF/serum ratio of 0.52 was measured throughout the timecourse of the trials.^{14, 35} About 45% of the drug is protein bound in plasma, and the volume of distribution is 10 L/kg, indicating substantial distribution out of the central compartment.^{2, 34}

The half-life of elimination in man is very long, and the 58 h half-life reported by Almeida *et al.*³⁴ was consistent with the 60-80 h values reported by Sonkusare *et al.*,² and the “up to 100 h” half-life noted by Parsons *et al.*¹ About 75% of the drug is excreted in urine. Acidification of urine increases MEM clearance, but urine flow rate does not have a significant effect.³⁶ Taken together with the low rate of hepatic clearance of the drug, dose adjustment may be appropriate for renally impaired patients, but not necessarily for those with liver insufficiency.

Fewer pharmacokinetic studies were done in animal models, and no detailed animal experiments were conducted that allow calculation of pharmacokinetic parameters as were done in human. A review¹⁴ indicated that most of the acute dosing studies used i.p. administration in the rat, and far higher doses were required to reach the therapeutic levels found in humans. The major factor in the difference between the pharmacokinetics in rat and human was the long half-life of elimination in human (50 h or more) compared to the 3-5 h half-life in rat.¹ Accordingly, infusion using minipumps was employed in experiments. Infusion for 7-day at 20 mg/kg/day to rats resulted in a concentration in extracellular fluid of brain of $0.83 \mu\text{M}$, a therapeutically significant concentration.³⁷ Quack *et al.*³⁸ found that i.p. doses of 5-10 mg/kg in rat led to plasma concentrations of 1-3 μM , and doses of 10 and 20 mg/kg resulted in C_{max} levels in the CNS of 1.2 and $2.6 \mu\text{M}$, respectively. Danysz *et al.*,¹⁶ found levels of 1 and $5.5 \mu\text{M}$ 60 min after i.p. dosing of 5 and 10 mg/kg MEM, respectively.

MEM was generally described as “poorly metabolized” in humans, with 57-82% excreted unchanged.^{34, 39} Similarly, Sankusare *et al.*² noted that 75% of the dose was excreted unchanged in humans. Those same authors noted that there is little hepatic metabolism, so hepat-

ic impairment is not likely to change clearance of the drug. Renal clearance, however, is key to elimination of MEM. Therefore, the known competition of amantadine for transport by organic cation transporters in kidney suggest that the structurally-related MEM may also significantly impact drug clearance when co-administered with drugs that compete for efflux by this probenecid-sensitive transporter.⁴⁰ Change in urinary pH, but not flow rate, has marked effect on renal clearance of MEM.³⁶ Acidification of the urine greatly increases elimination of the strong base MEM.

The major metabolites of MEM in humans include 4- and 6-hydroxymemantine (hydroxylation of the methylene positions on the cyclohexane ring bearing the methyl groups and the amino group), as well as oxidation of the 1-amino group to nitroso.²

GC/MS analysis of tissues of a patient who died of a cause unrelated to treatment found the major analyte in brain to be unmetabolized MEM (1-2 μM); the concentration of MEM in blood was about 0.3 μM .³⁹ The major metabolite was determined to be that from the hydroxylation of the 3-methyl group, though more modern mass spectral techniques may have yielded different results than those published in 1980.

VIb. CNS Penetration

MEM penetrates into the CNS with facility, as demonstrated in both clinical and rodent studies. MEM crosses the blood-brain barrier rapidly, and within 30 min of an iv infusion the drug can be detected in the CSF of patients.² At a dose of 20 mg/day, the CSF levels reach relevant inhibitory concentrations at the NMDA receptor. Steady state concentrations of MEM reach 0.2 μM in the CSF of patients following doses of 20 mg/day for 11 days, and a CSF/serum ratio of 0.52 was measured throughout the time course of the trials.^{14, 35} In another study, the concentration of MEM in the brain of a patient who died of a cause unrelated to treatment was found to be 1-2 μM in brain, as measured in the temporal lobe, hypothalamus and pons, while the concentration in blood was about 0.3 μM .³⁹

Penetration of MEM into the brain was demonstrated by PET using an ¹⁸F analog of MEM; levels in brain peaked 30 min post injection in mice.⁴¹ In rats, i.p. administration of MEM (10 mg/kg) leads to plasma levels and free CNS concentrations in the 1 μM range.¹ In rats infused for 7 days with MEM (20 mg/kg/day), whole brain concentrations were 44 times that of free serum concentrations,³⁷ though much of the MEM in brain tissue may have been due to lysosomal sequestration.¹

VIc. Calculated log([brain]/[blood]) (Clark Model)⁴²

0.26

VII. Safety, Tolerability, and Drug Interaction Potential

VIIa. Safety and Tolerability

MEM was described as well-tolerated in the clinical studies published in the literature. This is likely due to the favorable faster open channel blocking/unblocking kinetics that are key in efficacy endpoints, yet allow displacement of MEM in normal physiological functioning that results in low side effects.

The most common side effects found in one set of clinical trials (coadministered with donepezil) of three (166 patients) and six months duration (250 and 400 patients), were dizziness, headache, and constipation, and affected less than 10% of the subjects.⁴³ MEM monotherapy (10 mg b.i.d.) was well tolerated in 28-week studies²⁶. Greater than 90% of the subjects completed the study, and the most serious adverse events were injuries due to falls. A comprehensive review by Sonkusare *et al.*² noted that MEM was well tolerated in all trials, some extending out to one year, that included 2297 patients enrolled in 27 separate clinical trials.

Learning and Memory

Since long term potentiation (LTP), mediated through NMDA receptors, is key to the process of learning and memory, much of the literature dealt with determining if MEM would interfere with that process at therapeutic levels of the drug. MEM did not adversely effect LTP, and had “no negative effects on learning and memory.”^{1, 4, 8}

Abuse Potential.

The low abuse potential of MEM was demonstrated in preference studies with rats self administering cocaine,² as well as in monkeys and mice self administering phencyclidine.¹ This is consistent with the experience in clinical trials with MEM.²

General Toxicity: There was no evidence of carcinogenicity, genotoxicity or impairment of fertility with MEM in animal toxicity studies, but it has shown potential for reducing intrauterine growth in animals.²

VIIb. Drug Interaction Potential

MEM is described as “very poorly metabolized”,^{34, 39} perhaps consistent with the lack of inhibition of human cytochrome P450 (CYP) enzymes. MEM inhibited recombinant CYP2B6 at the clinically relevant K_i of 0.5 μ M, but showed no appreciable effect on CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 at therapeutically relevant concentrations.⁴⁴ Together these enzymes are responsible for the metabolism of >90% of pharmaceutical

agents, and it may be assumed that there is very low potential for drug interactions mediated by competition for CYP enzymes.

There was no pharmacokinetic interaction between the therapeutic acetylcholine esterase inhibitor donepezil and MEM (Adis R&D Insight). Renal clearance is a major route of elimination of MEM, and drugs like cimetidine, ranitidine, procainamide, quinidine, and nicotine use the same cationic renal transporter as does amantadine, suggesting that these drugs may also interact with MEM to increase its plasma concentration.⁴⁰

Jain³³ noted that “the following drugs given concomitantly may accentuate the effects and adverse reactions of MEM: barbiturates, neuroleptics, L-DOPA, dopamine agonists, and amantadine, but the author provided no detailed information as to the mechanism and specific drugs involved in the classes mentioned.

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