Memantine: Pharmacological properties and clinical uses

Kumar S

Neurology Unit, Department of Neurological Sciences, Christian Medical College Hospital, Vellore - 632004, India.

Memantine is a relatively new drug specially developed for use in moderate-to-severe dementia. It is an uncompetitive N-methyl-D-aspartate receptor antagonist and reduces glutamatergic excitotoxicity. Though Alzheimer’s disease (AD) is the commonest cause of dementia in the world, there is no “cure” available for the same. Cholinesterase inhibitors such as donepezil and rivastigmine have been shown to provide symptomatic relief in patients with AD but have no effect on disease progression or survival. Moreover, they are not helpful in more severe stages of dementia. Memantine has been shown to cause modest improvement in clinical symptoms in severe stages of AD and may retard the disease progression. Moreover, it has been shown to be useful in various forms of dementia including AD, vascular dementia and Wernicke-Korsakoff psychosis. It is also the first drug to cause complete disappearance of pendular nystagmus due to multiple sclerosis. The current review focuses on the pharmacological properties of memantine and examines the recent evidence in favor of memantine.

Key Words: clinical uses, dementia, memantine, neuropharmacological properties

Introduction

Alzheimer’s disease (AD) is a progressive neurological condition that usually presents with short-term memory impairment, and then progresses to profound cognitive and physical disability and is the commonest cause of dementia in the world. The diagnosis is based on clinical features; however, a definitive diagnosis requires histopathological examination of the brain. Patients with AD need round-the-clock supervision for their activities of daily living and pose a significant burden on family and caregivers. The financial problem of their loss of productivity is compounded by an enormous amount of expenditure incurred on their care. Currently, there is no ‘cure’ possible for AD. However, various drugs are used for symptomatic treatment that include cholinesterase inhibitors (such as donepezil, rivastigmine and galantamine), vitamins, antidepressants and antipsychotics. The current review focuses on memantine that differs from other drugs used in dementia in terms of its mechanism of action. Memantine is a low- to moderate-affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, which reduces glutamatergic excitotoxicity. Memantine has been approved in Europe in 2002, and United States in October 2003 for treatment of moderate to severe AD. In addition, memantine has been found to be useful in other forms of dementia and some forms of acquired nystagmus.

Neuropharmacological basis for its use in the treatment of AD

The neurobiological basis for the therapeutic activity of memantine in AD is not fully understood. However, it is not a cholinesterase inhibitor and therefore, is different from the drugs currently used for AD. Memantine’s mechanism of action is a voltage-dependent, low-moderate affinity, uncompetitive NMDA receptor antagonism with fast-blocking/unblocking kinetics. The low-moderate affinity is important because other NMDA receptor antagonists, such as ketamine and amantadine, are high-affinity compounds with neuropsychiatric side-effects. The fast on/off kinetics are also important because this means that memantine sits on the receptor just long enough to prevent pathologic activation of the glutamate receptors and then quickly goes away when physiologic activation of the glutamate receptors is needed. Memantine blocks the effects of abnormal glutamate activity that may lead to neuronal cell death and cognitive dysfunction. The fast on/off kinetics and low-moderate affinity are the key to memantine action because it blocks the effects of excessive glutamate while preserving physiologic activation of NMDA receptors required for learning and memory. Like other NMDA receptor antagonists, memantine at high concentrations can inhibit mechanisms of synaptic plasticity that are believed to underlie learning and memory. However, at lower, clinically relevant conc...
centrations memantine can promote synaptic plasticity and preserve or enhance memory in animal models of AD.\(^2\) In addition, memantine can protect against the excitotoxic destruction of cholinergic neurons. However, it should be remembered that both cholinergic and glutamatergic approaches to AD are based on hypotheses and not proven.

NMDA-receptor-dependent excitotoxicity plays a major role in progressive neuronal loss seen in dementia and the weak NMDA-receptor blocking property of memantine may confer protection against the excitotoxic destruction of neurons. However, it should be remembered that both cholinergic and glutamatergic approaches to AD are based on hypotheses and not proven.

Clinical indications

1. Severe dementia: Though the first study on the usefulness of oral memantine in dementia was published in 1991,\(^3\) the recent interest occurred after a 1999 trial.\(^4\) In a randomized placebo-controlled trial on about 150 patients with dementia (comprising AD and vascular dementia), the treatment group received memantine at a dose of 10 mg/day for 12 weeks. The memantine-treated group was noted to have a significantly better functional outcome and reduced care dependence as compared to the group that received placebo. (Level of evidence: Ib; Grade of recommendation: A).

2. Vascular dementia (VaD): In a multicentric randomized, double-blind, placebo-controlled trial in UK\(^5\) involving about 580 patients with VaD with mini-mental status examination (MMSE) score between 10 and 22, the treated group received memantine at a dose of 20 mg/day for 28 weeks. This group was noted to have a significantly improved cognition as compared to the group receiving placebo. Similar improvement was noted in a multicentric study conducted in France.\(^6\) (Level of evidence: II; Grade of recommendation: B).

3. Moderate-to-severe AD: In a multicentric randomized, double-blind, placebo-controlled trial in the US\(^7\) about 250 patients with moderate-to-severe AD were treated with either memantine at a dose of 20 mg/day or placebo for 28 weeks. The treatment group was found to have reduced clinical deterioration and better functional status. (Level of evidence: Ib; Grade of recommendation: A).

4. Dementia of Wernicke-Korsakoff syndrome (WKS): In a recent trial, 16 patients with dementia due to WKS were treated with either memantine (10 mg twice daily) or placebo for 28 weeks.\(^8\) At follow-up, the group receiving memantine had a significantly better cognitive and functional outcome. (Level of evidence: III; Grade of recommendation: B)

5. Acquired pendular nystagmus (APN) of multiple sclerosis: There is no specific therapy for APN due to multiple sclerosis. However, in a recent trial, all 11 patients with this condition treated with memantine had complete cessation of nystagmus compared to poor response in patients treated with scopolamine.\(^9\) (Level of evidence: III; Grade of recommendation: B)

The trials described provide Class Ib evidence of efficacy of memantine monotherapy in treating AD. As the mechanism of action of memantine differs from the widely used cholinesterase inhibitors, combination therapy could be complementary or synergistic. In fact, this issue was addressed in a recently published trial.\(^10\) In a multicentric trial, about 400 patients with moderate-to-severe dementia (with MMSE scores of 5 to 14) on stable doses of donepezil, were randomized to receive either memantine (starting at 5 mg/day, increased to 20 mg/day) or placebo. Memantine treatment resulted in significantly better outcomes than placebo on measures of cognition, activities of daily living, global outcome, and behavior.

Dosage and administration

Memantine (available as memantine hydrochloride) is administered orally at an initial dose of 5 mg once daily. The dose is increased in weekly increments of 5 mg daily to a dose of 20 mg daily (10 mg twice daily) is reached. Memantine hydrochloride is well absorbed following oral administration, with peak plasma concentrations achieved in about 3–7 hours. Memantine is eliminated principally in urine, with approximately 57–82% of an administered dose excreted as unchanged drug; the remainder of the dose is converted to metabolites that exhibit minimal NMDA receptor antagonist activity.

Adverse events

Memantine is well tolerated and safe as shown in all the reported trials.\(^3,10\) The commonest side-effect noted was dizziness. It is also well tolerated when co-administered with cholinesterase inhibitors for treating AD.\(^10,11\)

Cost-effectiveness analysis

Memantine (as compared to placebo) is reported to cause a reduction in resource utilization (including caregiver costs) and total health costs.\(^12\) This effect was seen despite the direct cost being higher in the memantine group (due to the cost of memantine). The study also showed favorable effects of memantine on time to institutionalization and institutionalization at week 28 of treatment.

Conclusions

There is convincing evidence available for recommending the use of memantine in the treatment of AD; however, further well-designed randomized controlled trials are required to determine its usefulness in treating VaD and WKS. It can be used as a monotherapy or in combination with cholinesterase inhibitors. It is well tolerated and reduces the overall cost of treatment/care.
References


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