Current Psychiatry

Out of the pipeline

Memantine

New option for advanced Alzheimer's

NMDA receptor antagonist targets functioning, is well-tolerated, and may be combined with cholinesterase inhibitors.

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As America's population ages, the need to find new treatments for Alzheimer's disease (AD) is increasingly urgent. Agents that have reached the medical mainstream in recent years target the disease in its mild to moderate stages. Memantine recently gained FDA approval for treating moderate to severe AD.

HOW IT WORKS

Memantine is an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist. NMDA receptors mediate the effects of the excitatory amino acid glutamate, promote entry of calcium through ion channel pores, and are essential for normal learning and memory.[1] Prolonged excessive glutamate stimulation, however, can lead to excitotoxicity and nerve cell death.

High-affinity NMDA receptor antagonists cause unacceptable side effects in humans and have not been well tolerated in clinical trials. By contrast, memantine—a moderate- to low-affini-

Table

Memantine: Fast facts

Drug brand name:
Namenda

Class:
NMDA receptor antagonist

FDA-approved indication:
Moderate to severe Alzheimer's disease

Approval date:
Oct. 17, 2003

Manufacturer:
Forest Pharmaceuticals

Dosing forms:
5 mg, 10 mg ("titration packets" containing 5-mg and 10-mg tablets are available)

Recommended dosage:
Begin at 5 mg/d for 1 week; increase to 5 mg bid the second week, then to 10 mg in the morning and 5 mg in the evening for the third week; increase to 10 mg bid for continued dosing

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ty NMDA receptor antagonist with rapid blocking/unblocking kinetics—has been well tolerated in clinical trials. The agent is readily displaced by presynaptic stimuli to allow normal channel function, but it reduces calcium influx from chronic low-amplitude glutamate stimulation.[2]

Memantine's voltage-dependent characteristics allow it to block low-level tonic pathologic activation of NMDA receptors caused by low glutamate concentrations. This property also allows physiologic activation of receptors after synaptic release of larger glutamate concentrations that produce membrane depolarization.[2] Memantine has demonstrated neuroprotection of neurons exposed to glutamate in a variety of in-vitro preparations.[3]

In experimental models, memantine has been shown to prolong long-term potentiation, a neurophysiologic correlate of learning and memory. Rats treated with memantine show enhanced learning recovery following entorhinal cortex lesions.[3]

Memantine is not likely to interact with drugs metabolized by cytochrome P-450 enzymes

Memantine has been shown to protect cholinergic cells in both acute and chronic animal models. It also prevents pathologic changes in the hippocampus produced by direct injection of beta-amyloid protein.[3] These findings suggest that memantine may improve learning and memory and may have neuroprotective properties in AD.

PHARMACOKINETICS

Memantine is absorbed completely from the GI tract and reaches maximum serum concentration in 6 to 8 hours. It is widely distributed and passes the blood-brain barrier with CSF concentrations approximately one-half those of serum levels. Dosages between 5 and 30 mg/d result in serum levels of 0.025 to 0.529 mmol. Relatively little biotransformation occurs.

The agent's half-life ranges between 75 and 100 hours.[4] Memantine is 10% to 45% protein bound, and 80% of circulating memantine is present as the parent compound. These kinetics justify once-daily dosing, although memantine usually is given bid.

Three metabolites have been identified, none of which exhibit NMDA receptor antagonist activity. Memantine minimally inhibits cytochrome P-450 enzymes, so interactions with drugs metabolized by these enzymes are unlikely.[5]

Memantine may potentiate the effects of barbiturates, neuroleptics, anticholinergics, L-dopa, ketamine, amantadine, dextromethorphan, and dopaminergic agonists. Concomitant use of memantine and amantadine should be avoided because the compounds are chemically related and both are NMDA antagonists. Memantine may hinder the effects of dantrolene or baclofen, so doses of these agents may need to be adjusted upward.

Memantine is eliminated almost completely via renal cation transport proteins. Drugs that use the same transport system—such as cimetidine, ranitidine, procainamide, quinine, and nicotine—may interact with memantine, possibly leading to increased plasma levels of these agents.

Hydrochlorothiazide activity is reduced by 20% when memantine is co-administered. Sodium bicarbonate, carbonic anhydrous inhibitors, and other drugs that alkalinize the urine may reduce memantine clearance and increase its serum levels.[4]

In healthy elderly volunteers with normal and reduced renal function, researchers observed a significant correlation between creatine clearance and total renal clearance of memantine, suggesting that patients with renal disease may require lower dosages.[5]

EFFICACY

In a preliminary, placebo-controlled study[7] of patients with vascular- or Alzheimer's-type

dementia, memantine was associated with improved Clinical Global Impression of Change and Behavioral Rating Scale for Geriatric Patients scores. Mini-Mental State Examination (MMSE) scores for all patients entering the study were <10, indicating severe cognitive impairment. Global measures improved in 61 of 82 (73%) patients taking memantine, 10 mg/d, and in 38 of 84 (45%) patients taking placebo. Care dependence improved 3.1 points in the memantine group and 1.1 points in the placebo group.

Data show combination cholinesterase inhibitor/ memantine therapy to be clinically safe

Reisberg et al[8] gave memantine, 20 mg/d, or placebo to 252 patients with AD across 28 weeks. The memantine group performed at significantly higher functional levels than the placebo group on the Alzheimer's Disease Cooperative Study ADL Scale and the Severe Impairment Battery (SIB). The differences on the Clinical Interview-Based Impression of Change with caregiver input (CIBIC-plus) scale were nearly significant ($p = 0.06$). Patients entering the study had MMSE scores between 3 and 14. The magnitude of drug-placebo difference was modest (approximately 6 points on the SIB).

In a third pivotal trial, 403 patients with AD were randomly assigned to memantine, 20 mg/d, or placebo across 24 weeks. All patients were also taking the cholinesterase inhibitor donepezil, 10 mg/d.[9] The memantine/donepezil group scored higher than the placebo/donepezil group on several scales. MMSE scores at entry ranged from 5 to 14. Drug-placebo differences were similar in magnitude to those observed in earlier studies.

TOLERABILITY

Controlled trials of memantine in patients with AD demonstrated few adverse effects.

Reisberg et al[8] reported that 84% of memantine-group patients and 87% of the placebo group experienced adverse effects. More placebo-group than memantine-group patients (17% vs. 10%) discontinued the study because of adverse events. Agitation was the most commonly cited reason for discontinuation (7% of the placebo group and 5% of those taking memantine). No adverse event was significantly more common in the memantine group.

Tariot et al[9] noted that confusion and headache were somewhat more common among those receiving memantine versus placebo. In other studies, symptoms possibly related to memantine included headache, akathisia, insomnia, increased motor activity, and excitement.[6, 10-12]

CO-ADMINISTRATION WITH CHOLINESTERASE INHIBITORS

The range of AD severity targeted by memantine overlaps that addressed by the cholinesterase inhibitors donepezil, galantamine, and rivastigmine, which are indicated for mild to moderate AD. Many patients will receive both memantine and a cholinesterase inhibitor.

Data show this combination therapy to be clinically safe. Tariot et al[9] found no increase in adverse events when memantine was co-administered with donepezil. Post-marketing surveillance studies in Germany indicate low rates of adverse events among patients receiving a cholinesterase inhibitor and memantine.[13] In-vitro laboratory data indicate that memantine does not affect or interact with cholinesterase inhibition.[14]

Memantine is not metabolized by liver enzymes. No interaction with antidepressants or antipsychotics commonly used in AD is anticipated.

CLINICAL IMPLICATIONS

Memantine, with a mechanism of action different from that of existing agents, offers a new

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avenue of therapeutic intervention and expands the spectrum of patients who may benefit from FDA-approved drug therapy.

Research is needed to determine whether memantine is useful in earlier stages of AD and in treating mild cognitive impairment. The role of glutamate excitotoxicity in AD also needs to be defined.

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Related resources

- Alzheimer's Association. www.alz.org
- Mendez M, Cummings JL. *Dementia: a clinical approach* (*3rd ed*). Boston: Butterworth Heinemann, 2003.

DRUG BRAND NAMES

Amantadine • Symmetrel
Cimetidine • Tagamet
Dantrolene • Dantrium
Donepezil • Aricept
Galantamine • Reminyl
Memantine • Namenda
Procainamide • Procanbid
Procainamide • Exelon

DISCLOSURE

The author has received research/grant support and/or is a consultant to AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Eisai Pharmaceuticals, Eli Lilly and Co., Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica, Novartis Pharmaceuticals Corp., and Pfizer Inc.

Memantine offers clinicians a drug treatment option for moderate to severe Alzheimer's disease. In clinical trials, the agent has demonstrated efficacy and tolerability when used alone or with cholinesterase inhibitors.

Bottom Line