PharmaNote®

Volume 19, Issue 5 February 2004

Memantine (Namenda®) A new option FOR alzheimer's disease

Fani Lane, Pharm.D. Candidate

Introduction

Alzheimer's Disease (AD) is a neurodegenerative disorder estimated to affect 4 to 8% of the population over age 65 and up to 20% of those over age 85 in Europe. Its incidence is increasing substantially as the population ages and the number diagnosed is predicted to double for every six years of life expectancy.[1] About 4 million Americans, 90% of whom are age 65 and older, have Alzheimer's disease. Unless prevention or a cure is found, the number of Americans with AD could reach 14.3 million 50 years from now.[2]

The theory that AD and the resulting typical cognitive and functional impairments are due primarily to a cholinergic brain deficit is increasingly challenged by the glutamatergic hypothesis of dementia. The strength of that hypothesis is based on the following facts: glutamate is the main fast excitatory neurotransmitter in the regions associated with cognition and memory (cerebral cortex and hippocampus), cortical and subcortical structures that contain glutamatergic receptors are structurally damaged during the course of AD, glutamate acts as an excitotoxin (causing neuronal death when excessive levels are chronically released), the neurochemical changes and some of the clinical symptoms seen in dementia can be induced experimentally with excitotoxins (quinolinic acid or N-methyl-D-aspartate), and clinical signs of dementia correlate with deficits of glutamatergic association fibers.

Memantine is a blocker of glutamate gated N-methy-D-aspartate (NMDA) receptor channels, which allows the physiological activation of NMDA receptors during memory formation while blocking their pathological activation. This property is due to the rapid, voltage-dependent nature of the interactions of memantine with the NMDA receptor channel.[3] Memantine was approved in Europe in May of 2002. There it is marketed under the name Ebixa® by Merz Pharmaceuticals. In the U.S., the product was approved in October of 2003 and is marketed under the name Namenda® by Forest Laboratories. This article will examine the safety, efficacy, and tolerability of memantine.

Pharmacology and Pharmacokinetics

Glutamatergic neurons form the major excitatory system in the brain and play a pivotal role in many physiological functions. Glutamate activates several receptors such as the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and the N-methyl-D-aspartate (NMDA) receptors. The later have three cardinal features: high permeability to Ca^{2+} ions; voltage-dependent block by Mg^{2+} ions; and slow gating kinetics. Physiologically, NMDA receptors are transiently activated by mM concentrations of glutamate, whereas during

INSIDE THIS ISSUE:

Table 1. Results of the efficacy analysis[7*]

Measure	Base Line		Analysis with Last Observation Carried Forward[†] (Change from Base Line at End Point)			Analysis of Observed Cases[‡] (Change from Base Line at Week 28)		
	MNT	Placebo	MNT	Placebo	*p*[§]	MNT	Placebo	*p*[§]
CIBIC-Plus Score	NA (N=126)	NA (N=126)	4.5±1.12 (N=118)	4.8±1.09 (N=118)	0.6	4.4±1.12 (N=97)	4.7±1.13 (N=84)	0.03
ADCS-ADLsev Score	26.8 (N=126)	27.4 (N=126)	-3.1±6.79 (N=124)	-5.2±6.33 (N=123)	0.02	-2.5±6.27 (N=97)	-5.9±6.78 (N=84)	0.003
SIB Score	65.9 (N=126)	68.3 (N=126)	-4.0±11.34 (N=124)	-10.1±13.5 (N=123)	<0.001	-4.5±11.48 (N=96)	-10.2±12.66 (N=83)	0.002

MNT=memantine, CIBIC-Plus=Clinician's Interview-Based Impression of Change Plus Caregiver Input, NA=not applicable, N=number of patients, ADCS-ADLsev=Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory modified for severe dementia, SIB=Severe Impairment Battery.
[*]Plus-minus values are means ±SD (standard deviation).
[†]The analysis with the last observation carried forward was performed with the intention-to-treat population.
[‡]The observed-cases analysis was performed with 181 patients observed at week 28.
[§]p-values are based on the Wilcoxon-Mann-Whitney test for between-treatment comparisons.

pathological activation such as that occurring in AD, NMDA receptors are likely activated by lower concentrations of glutamate but more or less continuously. This overactivation of glutamate receptors and continuous Ca^{2+} influx ultimately leads to both cognitive deficits and neuronal loss in neurodegenerative dementia.[4] Blockade of NMDA receptors by memantine slows the intracellular calcium accumulation and helps to prevent further nerve damage. With a low affinity for NMDA-type receptors, memantine may prevent excitatory amino acid neurotoxicity without interfering with the physiological actions of glutamate required for memory and learning. *In-vitro* studies demonstrate that memantine lacks affinity for most serotonin receptor subtypes (except $5HT_3$), muscarinic acetylcholine, α and β adrenergic, dopaminergic, histaminic, and glycine receptors. Memantine appears to have antagonist activity at the $5HT_3$ receptor and affinity for nicotinic acetylcholine receptors, but the clinical impact of these associations are not yet defined.[5]

Memantine is well absorbed after oral administration and has linear pharmacokinetics over the therapeutic dose range. Following oral administration, memantine is highly absorbed with peak concentrations reached in about 3-7 hours. Food has no effect on the absorption of memantine. Its mean volume of distribution is 9-11 L/kg and the plasma protein binding is low (45%). Memantine undergoes little metabolism, with the majority (57-82%) of an administered dose excreted unchanged in urine; the remainder is converted primarily to three polar metabolites with minimal NMDA receptor antagonist activity. The hepatic microsomal CYP450 enzyme system does not play a significant role in the metabolism of memantine. Memantine has a terminal elimination half-life of about 60-80 hours. Renal clearance involves active tubular secretion moderated by pH dependent tubular reabsorption.[6]

Clinical Trials

The effectiveness of memantine as a treatment for patients with moderate-to-severe Alzheimer's disease was evaluated in 2 randomized, double-blind, placebo-controlled clinical studies (Studies 1 and 2) conducted in the United States that assessed both cognitive function and day-to-day function. The mean age of patients participating in these two trials was 76 with a range of 50-93 years. Approximately 66% of patients were female and 91% of patients were Caucasian. A third study (Study 3), carried out in Latvia, enrolled patients with severe dementia, but did not assess cognitive function as a planned endpoint.[3,7,8]

The studies utilized different clinical scales, such as the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus), the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory modified for severe dementia (ADCS-ADLsev), and Severe Impairment Battery (SIB) to evaluate the outcome measures. Clinical global scales are interview based and in-

Table 2. Primary endpoint CGI-C: results after 4 and 12 weeks[3] [*]

Follow-up	Outcome	Memantine		Placebo	
		N	%	N	%
Visit 3 (week 4)	Response[†]	48	59	34	40
	Non-response[‡]	34	41	50	60
Visit 5 (week 12)	Response[†]	60	73	38	45
	Non-response[‡]	22	27	46	55

CGI-C=Clinical Global Impression of Change, N=number of patients.
[*]Intention-to-treat analysis, N=166. [†]Response=improvement categories. [‡]Non-response=no change and deterioration categories, p<0.001 stratified Wilcoxon test.

clude information obtained from either the caregivers or directly from the patient. Patients with progressive dementia invariably evolve to a stage where they can no longer be tested by standard neuropsychological tests. The validity and reliability of scales such as the ADCS and SIB have been tested in clinical trials, hence their popularity among practitioners.[9,10]

Study 1 (Twenty-Eight-Week Study)

Patients with moderate-to-severe Alzheimer's disease were randomly assigned to receive placebo or 20 mg of memantine daily for 28 weeks. The primary efficacy variables were the CIBIC-Plus and the ADCS-ADLsev. The secondary efficacy end points included the SIB and other measures of cognition, function, and behavior. Two hundred fifty-two patients (67% women; mean age, 76 years) from 32 U.S. centers were enrolled. Of these, 181 (72%) completed the study and were evaluated at week 28. The base-line scores and the results based on analyses with the last observation carried forward and analyses of observed cases for the efficacy variables are shown in Table 1. Patients receiving memantine had a better outcome than those receiving placebo, according to the results of the CIBIC-Plus (p=0.06 with the last observation carried forward, p=0.03 for observed cases), the ADCS-ADLsev (p=0.02 with the last observation carried forward, p=0.003 for observed cases), and the SIB (p<0.001 with the last observation carried forward, p=0.002 for observed cases).[7]

Study 2 (Twenty-Four-Week Study)

Four hundred and four patients with moderate-to-severe AD with Mini-Mental State Examination scores of 5 to 14 who had been treated with donepezil for at least 6 months and who were still receiving a stable dose of donepezil were randomized to receive memantine (starting dose 5 mg/d, increased to 20 mg/d, n=203) plus donepezil or placebo plus donepezil (n=201) for 24 weeks. The primary outcome measure was the change from baseline on the SIB measure of cognition and on modified 19-item AD Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL19). The change in total mean scores favored memantine/donepezil vs. placebo/donepezil treatment for SIB (score range 0-100, p<0.001) and for ADCS-ADL19 (score range 0-54, p=0.03).[8]

Study 3 (Twelve-Week Study)

Dementia was defined by Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) criteria and severity was assessed by the Global Deterioration Scale (stages 5-7) and the Mini-Mental State Examination (<10 points). Primary endpoints were the Clinical Global Impression of Change (CGI-C) rated by the physician, and the Behavioral Rating Scale for Geriatric Patients (BGP), rated by the nursing staff. Care-dependent in-patients of both genders were considered for enrolment if aged between 60 and 80 years. Eighty-two patients were randomized to memantine treatment (5 mg/day during the first week and 10 mg/day during the next 11 weeks), while 84 patients took placebo. Results of the CGI-C are shown in Table 2. Results of the BGP-subscore per visit and pre-post changes (visit 5 versus visit 1) are given in Table 3. Treatment differences between the two groups are statistically significant in favor of memantine (p=0.016). In summary, the results of this trial support the hypothesis that memantine treatment leads to functional improvement and reduces care dependence in severely demented patients.[3]

Table 3. Primary endpoint BGP subscore: results per visit and pre-post changes[3] [*]

Visit	Memantine		Placebo	
	Mean ± SD	Min/Median/Max	Mean ± SD	Min/Median/Max
1	21.3±7.6	6/20.5/38	21.8±7.7	8/21/38
2	20.8±7.5	6/19.5/38	21.2±7.6	8/20/38
3	19.3±7.5	3/18/38	20.5±7.9	7/19.5/42
4	17.4±8.5	1/16/37	18.9±8.3	2/18/37
5	15.6±8.8	1/13.5/37	18.1±9.4	3/17/38
Change visit 5 vs. 1	-3.1±12.2	-24/-5/46[†]	-1.1±11.8	-17/-2/46[†]

BGP=Behavioral Rating Scale for Geriatric Patients, SD=standard deviation, Min/Max=minimum/maximum changes.
*Intention-to-treat analysis (N=166). [†]Worst case replacement, p=0.016, stratified Wilcoxon test.

Dosing and Administration

Memantine is FDA-approved for the treatment of symptoms of moderate-to-severe Alzheimer's disease or for the symptoms of dementia associated with mild-to-moderate vascular dementia. Tablets can be administered orally with or without food. The initial dosage for adults and the elderly is 5 mg once daily titrated slowly over 3 weeks. The dose should be increased by 5 mg/week over a 3-week period to a target dose of 10 mg twice daily at week 4. The maximum daily dose is 20 mg/day and it takes roughly 15 days to reach steady state plasma concentrations.

Periodic evaluation after initiation and during continuation of therapy may be helpful to the clinician in deciding treatment duration (i.e., continue treatment if improvement or stability in functional, cognitive or behavioral status continues). Memantine is not indicated for adolescents and children. Memantine elimination does not appear to be reduced in patients with hepatic impairment; no specific dosage adjustments are needed. Dosage adjustments are required in patients with severe renal impairment. However, specific guidelines are not available. Dosage adjustments are not required in patients with mild-to-moderate renal impairment. Until further data are available, avoid use in patients with renal failure.[3,6,7,8]

Toxicity and Safety

Memantine is contraindicated in patients with known hypersensitivity to memantine hydrochloride (HCl) or to any excipients used in its formulation. In clinical trials, seizures occurred in 0.2% of patients treated with memantine and 0.5% of patients treated with placebo. Co-administration of memantine with the acetylcholinesterase (AchE) inhibitor donepezil HCl did not affect the pharmacokinetics of either compound.

Because memantine is eliminated in part by tubular secretion, co-administration of drugs that use the same renal cationic system, including hydrochlorothiazide (HCTZ), triamterene (TA), cimetidine, ranitidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents. However, co-administration of memantine and HCTZ/TA did not affect the bioavailability of either memantine or TA, and the bioavailability of HCTZ decreased only by 20%. The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH>8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) and the clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Memantine should be used with caution under these conditions.[6]

In placebo-controlled trials in which dementia patients received doses of memantine up to 20 mg/day, the likelihood of discontinuation because of an adverse event was the same in the memantine group as in the placebo group. Table 4 lists treatment-emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled dementia trials and for which the rate of occurrence was greater for patients treated with memantine than for those treated with placebo.[3,6-8,11-12]

Table 4. Adverse events reported in clinical trials in at least 2% of patients receiving memantine[3,6-8,11-12]

Adverse Event	Placebo (N=922)	Memantine (N=940)
Body as a Whole		
Fatigue	1%	2%
Pain	1%	3%
Cardiovascular System		
Hypertension	2%	4%
Central and Peripheral Nervous System		
Dizziness	5%	7%
Headache	3%	6%
Gastrointestinal System		
Constipation	3%	5%
Vomiting	2%	3%
Musculoskeletal System		
Back pain	2%	3%
Psychiatric Disorders		
Confusion	5%	6%
Somnolence	2%	3%
Hallucination	2%	3%
Respiratory System		
Coughing	3%	4%
Dyspnea	1%	2%

Cost

The average retail price for a one-month supply of Namenda® 10 mg is $150.31 ($144.99-$152.99).

Summary

As the elderly population in the U.S. increases, there is a proportional increase in the social and economical impact of dementia, particularly its most common form, Alzheimer's disease. Dementia itself consists of a wide spectrum of diseases, ranging from the mild cognitive impairment that progresses through several clinical milestones to advanced dementia. Drugs that are currently available for the treatment of mild-to-moderate dementia have focused on providing patients with cholinergic substitution despite increasing amounts of data that challenge the cholinergic brain deficit theory. Recent clinical trials have shown the antiglutamatergic drug memantine to improve cognitive function in patients with vascular dementia and reduced care dependence in those with moderately severe to severe forms of the disease.

References

1. Mobius HJ. Memantine: update on the current evidence. Int J Geriatr Psychiatry 2003; 18: S47-S54.
2. National Institute on Aging. (1999). Progress Report on Alzheimer's Disease, 1999. National institutes of Health: Bethesda, MD.
3. Winblad B, Poritis N. Memantine in severe dementia: results of the 9M-Best Study (Benefit and efficacy in severely demented patients during treatment with memantine). Int J Geriatr Psychiatry 1999; 14: 135-146.
4. Danysz W, Parsons CG. The NMDA receptor antagonist memantine as a symptomatological and neuroprotective

treatment for Alzheimer's disease: preclinical evidence. Int J Geriatr Psychiatry 2003; 18: S23-S32.
5. Areosa SA, Sherriff F. Memantine for dementia. Cochrane Database Syst Rev 2003; (3): CD003154. In: Cochrane Library Issue 3, 2003. Oxford: Update Software.
6. Namenda [Package Insert]. St. Louis, MO; Forest Laboratories; 2003.
7. Reisberg B, Doody R, Stoffler A et al, for the Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003; 348: 1333-41.
8. Tariot PN, Farlow MR et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA 2004; 291(3): 317-24.
9. Panisset M et al. Severe impairment battery. A neuropsychological test for severe demented patients. Arch Neurol 1994; 51(1): 41-5.
10. Schneider LS et al. Validity and reliability of the Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997: 11 Suppl 2: S22-32.
11. Winblad B, Jelic V. Treating the full spectrum of dementia with memantine. Int J Geriatr Psychiatry 2003; 18: S41-S46.
12. Wilcock G, Mobius HJ, Stoffler A. A double-blind, placebo-controlled multicenter study of memantine in mild to moderate vascular dementia (MMM500). Int Clin Psychopharmacol 2002; 17(6): 297-305.

◆ ◆ ◆

Fosamprenavir calcium (Lexiva™) is a new protease inhibitor approved for the treatment of human immunodeficiency virus (HIV) infection in adults. It is a pro-drug of amprenavir with improved solubility over the parent drug providing patients the opportunity for a reduced pill burden. The usual dosage in antiretroviral-naive patients is 700 mg or 1400 mg taken once or twice daily, with or without ritonavir (to 'boost' fosamprenavir plasma concentrations). In protease inhibitor-experienced patients, the twice-daily administration regimen with ritonavir is required to assure viral suppression. Common side effects include: headache, flushing, rhinitis, dyspepsia, flu syndrome, back pain, dizziness, increased creatine kinase, and nausea.

Daptomycin (Cubicin™) is the first of a new class of antibiotics called cyclic lipopeptide antibacterial agents. It works by binding to bacterial membranes causing a rapid depolarization of the membrane potential which leads to inhibition of protein, DNA, and RNA synthesis resulting in bacterial cell death. It has been approved for the treatment of complicated skin and skin structure infections caused by susceptible strains of Gram-positive organisms including MRSA.

Alfuzosin (Uroxatral™) is a selective a_1-antagonist approved for the treatment of benign prostatic hyperplasia (BPH). The recommended daily dose is one 10-mg extended-release tablet given by mouth once daily. It should be used with caution in patients taking drugs that can inhibit or induce the cytochrome P450 3A4 isozyme and drugs which prolong the QT interval. Common adverse reactions include postural hypotension, dizziness, headache, fatigue, GI upset, and impotence.

The PharmaNote is Published by:
The Department of Pharmacy Services, UF Family Practice Medical Group, Departments of Community Health and Family Medicine and Pharmacy Practice
University of Florida