Efficacy and Safety of Memantine in Patients With Mild to Moderate Vascular Dementia
A Randomized, Placebo-Controlled Trial (MMM 300)

Jean-Marc Orgogozo, MD; Anne-Sophie Rigaud, MD, PhD; Albrecht Stöffler, MD; Hans-Jorgen Möbius, MD; Françoise Forette, MD

Background and Purpose—Based on the hypothesis of glutamate-induced neurotoxicity (excitotoxicity) in cerebral ischemia, this study examined the efficacy and tolerability of memantine, an uncompetitive N-methyl-D-aspartate antagonist, in the treatment of mild to moderate vascular dementia.

Methods—In this multicenter, 28-week trial carried out in France, 321 patients received 10 mg/d memantine or placebo twice a day; 288 patients were valid for intent-to-treat analysis. Patients had to meet the criteria for probable vascular dementia and have a Mini-Mental State (MMSE) score between 12 and 20 at inclusion. The 2 primary end points were the cognitive subscale of the Alzheimer Disease Assessment Scale (ADAS-cog) and the global Clinician’s Interview Based Impression of Change (CIBIC-plus).

Results—After 28 weeks, the mean ADAS-cog scores were significantly improved relative to placebo. In the intention-to-treat population, the memantine group mean score had gained an average of 0.4 points, whereas the placebo group mean score had declined by 1.6 points, ie, a difference of 2.0 points (95% confidence interval, 0.49 to 3.60). The response rate for CIBIC-plus, defined as improved or stable, was 60% with memantine compared with 52% with placebo (P = 0.227, intention to treat). Among the secondary efficacy parameters, which were analyzed in the per-protocol subset, MMSE was significantly improved with memantine compared with deterioration with placebo (P = 0.003). The Gottfries-Brane-Steen Scale intellectual function subscore and the Nurses’ Observation Scale for Geriatric Patients disturbing behavior dimension also showed differences in favor of memantine (P = 0.04 and P = 0.07, respectively). Memantine was well tolerated with a frequency of adverse events comparable to placebo.

Conclusions—In patients with mild to moderate vascular dementia, memantine 20 mg/d improved cognition consistently across different cognitive scales, with at least no deterioration in global functioning and behavior. It was devoid of concerning side effects. (Stroke. 2002;33:1834-1839.)

Key Words: cerebral ischemia ▪ dementia ▪ glutamate ▪ memantine ▪ N-methyl-D-aspartate ▪ randomized controlled trials

Alzheimer’s disease (AD) and vascular dementia (VaD) are the most common forms of dementia,1 but in contrast to AD, there is no drug licensed for the treatment of VaD, so its treatment is limited so far to the control of known vascular risk factors.

Glutamate is the principal excitatory amino acid neurotransmitter in cortical and hippocampal neurons.2 Accumulating evidence suggests that the cortical neuronal loss underlying dementia may be related to an increased sensitivity to glutamate and/or sustained elevations of glutamate levels.3 This leads to a cumulative influx of calcium into neurons, impaired neuronal homeostasis, and eventually neurodegeneration, resulting in cell death.4–6 One of the receptors activated by glutamate is the N-methyl-D-aspartate (NMDA) receptor, which is involved physiologically in learning and memory.7 Because excessive NMDA stimulation induced by ischemia leads to excitotoxicity,3 agents that block pathological stimulation of NMDA receptors might be anticipated to protect against further cortical neurodegeneration in VaD while the physiological function of the remaining neurons could be restored, resulting in symptomatic improvement.8

Memantine is a moderate-affinity, uncompetitive NMDA receptor antagonist that has been shown to have therapeutic potential in numerous central nervous system disorders without the undesirable side effects associated with many high-affinity NMDA receptor antagonists, which have failed so far in clinical development.9 Memantine has also been shown to prevent neurodegeneration and learning deficits in animal models of dementia and does not impair the physiological function of the NMDA receptor.10,11 In addition, memantine
reduces neuronal damage in global and focal animals models of brain ischemia. 12, 13

A number of clinical studies to date have shown memantine to improve cognition and functional performance in various stages of dementia. 14-18 The present study was designed to determine the efficacy and tolerability of memantine in patients suffering from mild to moderate VaD. The rationale for this trial was based on the reduction of neuronal damage caused by ischemia with memantine, 19 which may be expected to prevent progression of damage, and on its ability to normalize impaired glutamatergic neurotransmission, which may be expected to lead to symptomatic improvement. 20

Patients and Methods

Patients

Male and female patients ≥ 60 years of age with symptomatic mild to moderate VaD of 6 months’ duration were eligible to participate in the study. VaD was defined by the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) criteria 20 for probable VaD and a Modified Ischemic Score 21 (MIS) of ≥ 5. The NINDS-AIREN criteria, which include CT and/or MRI scan of the brain, require the presence of dementia and cerebrovascular disease and a temporal relationship between them. They were shown to be highly specific, especially when combined with the MIS. 22 The diagnosis of dementia of mild to moderate severity was established by participating investigators using the criteria of the Diagnostic and Statistical Manual of Mental Disorders (3rd edition, revised) 23 and by Mini-Mental State Examination (MMSE) 24 total scores of 12 to 20 at inclusion. Then, the assessment of CT or MRI scans by the local radiologist was used for inclusion. In addition, a central rating of the scans was performed to verify the eligibility criteria and to categorize the images for secondary subgroup analyses.

The main exclusion criteria were AD and secondary types of dementia, with the NINCDS-ADRDA criteria for AD, 25 by CT or MRI for structural causes other than VaD, and by checking appropriate laboratory parameters. Patients with a history of seizures, alcoholism, and/or drug abuse were also excluded, as well as chronic users of other medications with the potential to interfere with the study outcomes and patients suffering from psychotic episodes. The most frequent reasons for exclusion were CT or MRI scans not showing vascular lesions in the brain or laboratory values outside the predetermined ranges.

Patients gave written, informed consent to participate in this trial. Because the caregiver had to participate as a rater, his or her verbal agreement was also required before the enrollment of a patient. The study was conducted according to Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki and was approved by the relevant national (Center Hospitalier Universitaire Cochin, Paris) or local institutional review boards.

Study Design

This study was a phase 3, multicenter (50 centers), randomized, double-blind, parallel-group trial carried out between June 1996 and January 1999 in 48 centers in France and in 1 center each in Belgium and Switzerland. After a 2-week placebo run-in period, eligible patients were randomly allocated to receive memantine or placebo. After an initial 3-week titration period with 5 mg/d at week 1, 10 mg/d at week 2, and 15 mg/d at week 3 or matching placebo, patients received daily doses of 20 mg/d of memantine or placebo for the remainder of the 28 weeks of follow-up. Concomitant use of anticonvulsants, anti-Parkinson medications, centrally acting antihypertensives, hypnotics, anxiolytics, antipsychotics, and cognition enhancers was prohibited. Patients were assessed at baseline and at subsequent weeks 2, 4, 12, 20, and 28.

The trial had 2 primary end points. The first was a cognitive assessment using the cognitive subscale of the Alzheimer’s Disease Assessment Cognitive Scale (ADAS-cog). 26, 27 This scale was administered by a psychologist or speech therapist. ADAS-cog consists of 11 subtests that evaluate mainly memory, language, and praxis functions that provide a sum score from 0 (best score) to a maximum of 70 (worst score). The second was a global rating of change measured with the Clinician’s Interview Based Impression of Change (CIBIC-plus) that uses a score from 1 to 7 (1 = very much improved, 7 = very much worse). CIBIC-plus was performed by an independent physician blinded to the psychometric tests and incorporated input from the caregiver. 28 ADAS-cog was performed at baseline and at weeks 12 and 28. CIBIC-plus interviews were made independent of the ADAS-cog at baseline and at week 28.

Secondary efficacy variables included assessments of dementia severity by another cognitive test, the MMSE at baseline and at week 28, a composite instrument, the Gottsfries-Brane-Steen 29 (GBS) scale, and another global rating, the Clinical Global Impression of Change, 30 by the investigator at baseline and at weeks 12 and 28 and by the caregiver at week 28. Functional aspects were investigated with the Nurse’s Observational Scale for Geriatric Patients (NOSGER). 31

Safety and tolerability were assessed by the frequency of reported adverse events (AEs) and deviation from standard laboratory values at weeks 0, 12, and 28; ECG; vital signs; and physical examination at baseline and week 28.

Statistical Analysis

A sample size of 240 completers was calculated from the results of previous trials as the minimum necessary to detect a clinically meaningful difference to a power of 80% and an α risk of 5%. Therefore, assuming a nonadherence rate of 25% of all patients randomized, the number of patients to be enrolled was ~320, ie, 160 per group.

The intent-to-treat (ITT) population consisted of all randomized patients who received at least 1 dose of study medication and had at least 1 primary efficacy evaluation (CIBIC-plus or ADAS-cog) on treatment. For secondary variables, the per-protocol (PP) population was used. This included only those patients who completed the 28 weeks as planned and had measurements for all efficacy variables with no major protocol violations.

The confirmatory statistical analysis for the primary efficacy criteria CIBIC-plus and ADAS-cog was performed in the ITT population via hierarchical testing starting with a Cochran-Mantel-Haenszel test for CIBIC-plus, followed by an analysis of covariance (ANCOVA) for ADAS-cog. For CIBIC-plus, a dichotomized analysis with response/nonresponse had been predefined in the analysis plan; response was defined as any improvement or no change from baseline (scores of 1 to 4). Missing observations for the CIBIC-plus were replaced by the median score of 4 (ie, unchanged). For the ADAS-cog, missing values were replaced by use of the last observation carried forward (LOCF) method. For the other secondary end points, results were analyzed as observed cases (without replacement of missing observations) in the PP population.

Results

Patients

Of the 403 patients screened, 321 patients were randomly allocated, 165 to memantine and 156 to placebo treatment, and received at least 1 dose of study medication. Screen failures were due mainly to violation of the inclusion and/or exclusion criteria, with laboratory values and CT/MRI scans being the most frequent reasons. A total of 288 patients (80%), 147 on memantine and 141 on placebo, had at least 1 postbaseline efficacy assessment and were included in the ITT population. The most common reason for premature discontinuations were AEs, regardless of relationship to study...
TABLE 2. Main Efficacy Results: ITT-OC Analysis With No Replacement of Missing Visits or Items

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Memantine (Mean±SD)</th>
<th>Placebo (Mean±SD)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIC-plus at week 28</td>
<td>3.82±1.39</td>
<td>4.11±1.48</td>
<td>0.284</td>
</tr>
<tr>
<td>n</td>
<td>114</td>
<td>114</td>
<td></td>
</tr>
<tr>
<td>ADAS-cog, week 28–week 0</td>
<td>−1.25±5.32</td>
<td>1.58±6.42</td>
<td>0.0016</td>
</tr>
<tr>
<td>n</td>
<td>111</td>
<td>114</td>
<td></td>
</tr>
<tr>
<td>MMSE total scores, week 28–week 0</td>
<td>1.75±3.38</td>
<td>0.52±4.07</td>
<td>0.0121</td>
</tr>
<tr>
<td>n</td>
<td>105</td>
<td>108</td>
<td></td>
</tr>
<tr>
<td>CGI-C (physician) at week 28</td>
<td>3.58±1.09</td>
<td>3.85±1.19</td>
<td>0.0938</td>
</tr>
<tr>
<td>n</td>
<td>116</td>
<td>117</td>
<td></td>
</tr>
<tr>
<td>CGI-C (caregiver) at week 28</td>
<td>3.52±1.26</td>
<td>3.82±1.31</td>
<td>0.0921</td>
</tr>
<tr>
<td>n</td>
<td>115</td>
<td>118</td>
<td></td>
</tr>
<tr>
<td>NOSGER total score, week 28–week 0</td>
<td>2.73±11.67</td>
<td>3.26±12.95</td>
<td>0.8119</td>
</tr>
<tr>
<td>n</td>
<td>104</td>
<td>101</td>
<td></td>
</tr>
<tr>
<td>GBS total score, week 28–week 0</td>
<td>−0.36±15.38</td>
<td>3.38±16.34</td>
<td>0.1194</td>
</tr>
<tr>
<td>n</td>
<td>114</td>
<td>118</td>
<td></td>
</tr>
</tbody>
</table>

OC indicates observed cases.

* A posteriori probability values based on Mann-Whitney Wilcoxon test (2-sided).

advantage for the memantine patients over the placebo group.

Primary End Points

CIBIC-Plus

ITT-LOCF response rates at 28 weeks on CIBIC-plus were higher with memantine (n=88, 60%) compared with placebo (n=74, 52%), although this difference did not reach statistical significance (P=0.227). With the PP population, the absolute difference was larger (73% response with memantine versus 60% with placebo) and closer to—but still not reaching—statistical significance (P=0.08).

ADAS-Cog

Mean ADAS-cog total scores improved from baseline in the memantine group compared with a deterioration in the placebo group (the Figure). By week 28, memantine-treated patients had improved by a mean score of 0.4, while the placebo group had declined by 1.6 points overall in the ITT-LOCF analysis (absolute difference, 2 points). The 95% confidence interval (CI) for this difference was 0.49 to 3.60; ie, it did not overlap with 0. Even more favorable results were seen in the PP subset, with memantine patients improving by 1.0 point compared with placebo patients worsening by 1.4 points between baseline and week 28 (Δ=2.4 points; 95% CI =0, 0.77 to 4.05). Memantine was most effective in the more severely demented patients, as demonstrated by the results of an ANCOVA showing statistically significant effects of the ADAS-cog at baseline by treatment interaction (P=0.002) and with the baseline MMSE (P=0.0014).

Secondary End Points (All Analyses: PP Population)

MMSE total scores in placebo patients remained stable over the double-blind treatment period (mean change from baseline to 28 weeks, 0.2±4.24 points) and improved by 1.8±3.51 points in the memantine patients. The ANCOVA at week 28 showed a statistically significant (P=0.003) treatment effect on the MMSE (group difference, 1.717, least-squares mean).

The GBS scale showed a statistically significant difference between treatments at week 28, favoring memantine for the intellectual function subscore (P=0.04), but there was no significant difference in the motor function, emotional function, or different symptoms subscores (Table 3). One NOSGER items, disturbing behavior, showed a trend (P=0.07) in favor of memantine at week 28 (Table 4).

The CGI-C investigator rating showed a higher response rate (P=0.18) with memantine (80%) compared with pla-
TABLE 3. CGI-C Response at 28 Weeks: PP Population

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Memantine (n=93, n (%))</th>
<th>Placebo (n=95, n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>52 (56)</td>
<td>38 (40)</td>
</tr>
<tr>
<td>Stabilized</td>
<td>22 (24)</td>
<td>28 (30)</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>19 (20)</td>
<td>28 (30)</td>
</tr>
<tr>
<td>Caregiver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>47 (51)</td>
<td>42 (44)</td>
</tr>
<tr>
<td>Stabilized</td>
<td>24 (26)</td>
<td>21 (22)</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>22 (24)</td>
<td>32 (34)</td>
</tr>
</tbody>
</table>

Safety Results
Memantine was well tolerated, with a frequency of reported AEs comparable to that with placebo, 125 (76%) versus 115 (74%). The most frequently reported AEs were agitation (9 on memantine, 11 on placebo), confusion (8 on memantine, 9 on placebo), and dizziness (10 on memantine, 5 on placebo). A total of 38 memantine patients (23%) and 40 placebo patients (26%) experienced serious AEs. The most serious AEs were cerebrovascular events, in keeping with the pathophysiology of VaD. No type of serious AEs had a significantly higher incidence in the memantine group compared with the placebo group, and there were no treatment-related deaths during the study in either group. There were also no clinically significant effects of memantine on any biochemical markers or on blood pressure, heart rate, or ECG.

Discussion
More than one third of the patient population in this trial had neuoradiological signs of large cortico-subcortical stroke, whereas most (>80%) showed white-matter lesions and/or lacunes. Inclusion was restricted to the category of probable VaD patients according to the NINDS-AIREN criteria, whereas the NINCDS-ADRDA criteria were used to exclude AD patients. Both scales are well validated, but a possible contamination of the study sample with patients also having AD cannot be excluded because it remains quite difficult to exclude “mixed” cases, ie, those with overlapping VaD and AD pathology. In addition, from epidemiology and pathological evidence, a strict separation between these 2 main forms of dementia is often not possible and perhaps not justified because the 2 pathologies largely overlap in the elderly. In this context, it should be mentioned that positive results with memantine in the cognitive domains were also obtained in elderly patients with mild to moderate dementia and advanced AD and VaD.

After 28 weeks of treatment, there was an improvement relative to placebo of several end points in patients receiving memantine, as reflected in the clinical global ratings, which is considered clinically relevant. The confirmatory analysis of the dichotomized CIBIC-plus ratings failed to show statistical significance, but the clinical global rating of change, as assessed by the investigator as a secondary efficacy parameter, did reach statistical significance in favor of memantine.

In the cognitive domain, there was a statistically significant advantage of memantine over placebo in 2 different performance-based assessments, ADAS-cog (the Figure) and MMSE. The beneficial effect of memantine on cognitive function was further supported by the GBS intellectual function subscore, which also showed a statistically significant difference in favor of memantine.

From a methodological point of view, there is concern that ADAS-cog may not sufficiently capture the specific deficits of executive function in VaD patients and therefore may underestimate their dysfunctioning. However, the clinical criteria for AD and VaD are similar in construction and are based on common cognitive impairments that are similarly captured and quantified by ADAS-cog. Executive function, which may be particularly impaired in VaD, was not specifically assessed in this study because of the lack of instruments validated in clinical trials.

The magnitude of effect on cognition, as measured by ADAS-cog, was within the range reported for cholinergic drugs in AD, although the natural decline in VaD is thought to be slower than in AD, thus rendering the demonstration of a treatment effect in VaD more difficult. On the basis of the NINDS-AIREN criteria, VaD includes patients with discrete ischemic and hemorrhagic strokes, as well as those with lacunar and diffuse leukoencephalopathic ischemic lesions, and this heterogeneity may have compromised the magnitude of the effect of memantine. Whether restriction

TABLE 4. GBS Subscales: Mean Change From Baseline Plus SD for the PP Population

<table>
<thead>
<tr>
<th>Dimension</th>
<th>P*</th>
<th>Memantine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor function</td>
<td>0.874</td>
<td>0.58</td>
<td>1.39</td>
</tr>
<tr>
<td>Intellectual function</td>
<td>0.040</td>
<td>-0.74</td>
<td>1.73</td>
</tr>
<tr>
<td>Emotional function</td>
<td>0.333</td>
<td>-0.16</td>
<td>0.53</td>
</tr>
<tr>
<td>Different symptoms</td>
<td>0.301</td>
<td>-0.13</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Negative values represent improvement.
*Mann-Whitney U test for values at week 28.

TABLE 5. NOSGER Results by Dimension: Mean Change from Baseline for the PP Population

<table>
<thead>
<tr>
<th>Dimension</th>
<th>P*</th>
<th>Memantine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>0.614</td>
<td>0.45</td>
<td>0.61</td>
</tr>
<tr>
<td>IADL</td>
<td>0.321</td>
<td>1.05</td>
<td>0.34</td>
</tr>
<tr>
<td>ADL</td>
<td>0.931</td>
<td>0.40</td>
<td>0.19</td>
</tr>
<tr>
<td>Mood</td>
<td>0.647</td>
<td>0.99</td>
<td>0.86</td>
</tr>
<tr>
<td>Social behavior</td>
<td>0.325</td>
<td>1.49</td>
<td>0.92</td>
</tr>
<tr>
<td>Disturbing behavior</td>
<td>0.072</td>
<td>-0.36</td>
<td>0.38</td>
</tr>
</tbody>
</table>

IADL indicates independent activities of daily living. Positive values for change represent worsening.

*ANCOVA with the covariable baseline and center as a factor.
to a more specific subtype of VaD may result in a more favorable response of memantine remains to be tested, but the observed effect in this study is valid for all VaD patients as defined, ie, those with dementia associated with cerebrovascular disease for whom no specific treatment was available so far.

Only a few controlled clinical trials of VaD were published, and it is difficult to compare the results of the present study with those obtained with different compounds. One nimodipine trial was negative,41 and most trials with propentofylline40 did not use the ADAS-cog as an end point. In a trial with galantamine that included AD and VaD patients, the difference between groups in ADAS-cog change was reported to be 1.7 points for the VaD patients (H.R. Brashear, IPA Expert Meeting, Madrid, Spain, November 2001).

The results of the present study confirm previous studies with memantine in less well-defined patient populations,14–16 as well as a recent study of severe AD47 that also showed encouraging results in the cognitive domain. In parallel to the present study, a trial in VaD with a similar design performed in the United Kingdom also showed positive effects in the ADAS-cog (G. Wilcock, MD, et al, unpublished data, 2001).

This positive treatment effect on cognition is in accordance with the hypothesis that the glutamatergic system is involved in dementia and with the concept of neurotoxicity of glutamatergic overstimulation.6 The neuroprotective properties of memantine were demonstrated in various experimental settings.7–9 These properties may have contributed to the overall finding by slowing the progression of the dementia process,8,42,43 but with the very limited placebo decline in the present study, it is likely that a symptomatic improvement in cognitive performance was the main effect of memantine in these patients. This may be due either to a direct effect on cognition (“nootropic”) or to an enhancement of the mechanisms of recovery that occur naturally in patients with cerebrovascular lesions. To clarify this point, it would be interesting to test memantine in patients at the recovery phase of other manifestations of stroke for which no specific pharmacological treatment is available so far.

The present results confirm that pharmacological manipulation of the NMDA receptor with memantine is a promising avenue for treating patients with VaD. Earlier studies with memantine showed beneficial effects in various dementia populations, and the present study specifically demonstrates meaningful cognitive improvement with memantine in patients with mild to moderate VaD with very good tolerability.

Appendix

Memantine in Mild to Moderate VaD (MMM 300) Study Group

P. Baud, Nemours; J.M. Blard, Montpellier; M. Bouchacourt, Toulon; J. Boulliat, Bourg en Bresse; A. Bredin, Blaye; J.B. Cesari, Montpellier; P.H. Chapuy, Villeurbanne; J.P. Chartier, Rodex; J.P. Chartres, Bordeaux; M. Chatel, Nice; P. Clavelou, Chamalières; P. Contis, Colomiers; J.F. Dartigues, Bordeaux; S. De Boissiliers, Montpellier; P. De Faccq, Armentieres; R. Decombe, Troyes; G. Defer, Caen; J. Delorme, Lyon; H. Duclos, Pontoine; A. Engles, Roubaix; G. Fanjard, Castres; F. Forette, Paris (coordinating investigator); S. Frey, Clinical Development, Merz and Co, Frankfurt/M.; J. Gailledreau, Cachan; D. Gardeur, Paris (central review of scans); J.Y. Goas, Brest; R. Görtelmeyer, Biometrics, Merz and Co, Frankfurt/M.; O. Guard, Dijon; P. Lebrun-Grandie, Perigueux; J. Leche, Vendome; D. Leys, Lille; R. Meterau, Fontenay aux Roses; B. Michel, Marseille; L. Milandre, Marseille; P. Neuschwander, Lyon; J.M. Orgogozo, Bordeaux; M. Pages, Moissac; F. Pasquier, Lille; A. Pouliquen, Dieppe; A. Pouyet, Saint Brieuc; P. Pras, Nice; A.S. Rigaud, Paris; S. Rihet, Paris; R Rogez, Tours; T. Rosolacci, Maubeuge; A.M. Salandini, Nantes; L. Verdure, Rouen; F. Viallet, Aix en Provence; A. Vighetto, Lyon; N. Wazzan, Bastia; and Y. Wirth, Biometrics, Merz and Co, Frankfurt/M.

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