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Memantine induces reversible neurologic impairment in patients with MS

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ABSTRACT

Background: Cognitive dysfunction is very common in multiple sclerosis (MS) and it severely impairs patients' quality of life. Thus, we explored whether memantine might improve cognitive performance in patients with MS.

Methods: We conducted a pilot trial with memantine (30 mg/day) in patients with MS with cognitive impairment. The trial was designed as a 1-year, randomized, double-blind, crossover study comparing memantine against a placebo in 60 patients with MS and cognitive impairment. Cognitive impairment was defined as the performance 1.5 standard deviations below the normative data in at least two tests of two cognitive domains in the Brief Repeatable Battery–Neuropsychology. The primary endpoint was improvement of verbal memory and the secondary endpoints were safety and improvements in the other cognitive domains, disability and quality of life. The trial was registered at www.clinicaltrials.org: NCT00638833.

Results: Although 19 patients had been included, the trial was halted after nine patients reported a worsening of their neurologic symptoms that deteriorated their quality of life. Seven of the nine patients in the memantine arm had blurred vision, fatigue, severe headache, increased muscle weakness, walking difficulties, or unstable gait. Only two patients in the placebo group reported neurologic symptoms and in both cases they were related with changes in their disease-modifying therapy. The adverse events only occurred on reaching the maximum dose (30 mg/day). After stopping medication, the patients reverted to their baseline disability within a few days.

Conclusions: Memantine at a dose of 30 mg/day may induce transient worsening of neurologic symptoms of multiple sclerosis. Neurology® 2009;72:1630–1633

GLOSSARY

BRB-N = Brief Repeatable Battery-Neuropsychology; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; MSFC = MS Functional Composite; PR = progressive relapsing; RR = relapsing remitting; SP = secondary progressive.

Cognitive dysfunction is very common in multiple sclerosis (MS), occurring in up to 65% of patients.1-3 Because the symptoms of MS first appear in young adults with significant family and work commitments, cognitive impairment might have an important effect on their quality of life.4 However, there is currently no therapy to treat such cognitive symptoms. Memantine is a noncompetitive antagonist of NMDA receptors and it has been approved for the treatment of patients with Alzheimer disease.5 Memantine also appears to improve the symptoms of oscillopsia in patients with MS when administered at doses of up to 60 mg/day.6 Hence, we set out to test whether memantine is safe and if it improves cognitive performance in patients with MS.

METHODS We conducted a randomized, double-blind, placebo-controlled clinical trial in patients with MS using memantine (Ebixa), provided by Lundbeck SA, Denmark. The study was approved by the Institutional Review Board of the University of Navarra, the Navarra Ethical Committee for Clinical Research, and the Spanish Drug Agency. Patients were recruited by their

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Supported by an unrestricted grant from Lundbeck A/S, Denmark. The authors promoted and designed the study, recruited patients, collected, stored and analyzed the data, and wrote the paper independently of the sponsor.
Disclosure: The authors report no disclosures.
RESULTS The recruitment of patients began in October 2007 and by the time 19 patients had entered the study, 9 patients had had neurologic symptoms including blurred vision, fatigue, severe headache, increased muscle weakness, walking difficulties, or unstable gait. The family of one patient (ID# 5) reported cognitive deterioration, explaining that the patient was more disoriented and with less initiative than before. A new neuropsychological examination of this patient revealed moderate impairment in the BRB-N battery compared with the baseline assessment. Patient 2 had previously had optic neuritis and began to complain of blurred vision and increased brightness in the affected eye. Such symptoms remained until memantine administration was suppressed. Clinical examination did not reveal changes in visual acuity or in the visual field. However, low contrast visual acuity cards (Snellen cards) that are more sensitive in identifying visual acuity changes were not used and accordingly, we cannot rule out small changes in her visual acuity. Patients 4, 6, 11, and 17 had increased weakness in the limbs in which they had already experienced weakness with prior exacerbation, unstable gait, and greater physical fatigue. All of them displayed moderate to high disability, mainly due to the presence of moderate to severe paraparesis (EDSS 3.5–7). Clinical examination revealed slight decrease in muscle strength in the affected limbs and more unstable gait than at the previous examination, neither of which increased their EDSS score. Patient 15 had severe and continuous headache with occasional dizziness that disappeared a few days after suppressing the medication. She had not had migraine before, nor ataxia or dizziness. Patients 3 and 22 were unable to walk as far as before and they suffered greater physical fatigue. In all the patients who received memantine, the symptoms appeared once the full dose of 30 mg/day was reached.

Because patients fulfilling our inclusion criteria had moderate to severe disability (EDSS median: 4.23; range: 2–7), such complaints were initially attributed to pseudoexacerbations of the disease. We ruled out any other cause for neurologic impairment such as urinary infection, fever, the onset or change in the disease-modifying drugs administered, other therapies, or stressful events. In addition, we also ruled out changes in symptomatic therapies (i.e., baclofen). Due to the decrease in the patients’ quality of life, medication was reduced by 10 mg/day or stopped for 1 week. All patients reported the remission of their symptoms to their baseline performance within 24 to 48 hours of the reduction or suppression of the medication. Neurologic examination revealed similar neurologic signs as those established at the baseline. However, the patient with increased cognitive impairment did not return to baseline performance, suggesting that she might have suffered a progression of her disease. After reporting these unexpected adverse events to the Institutional Review Board of our institution and considering that a significant number of patients with neurologic impairment would drop out from the study, the blind element of the study was broken. As shown in the table, seven of the nine patients in the memantine group reported some degree of neurologic impairment during the trial and these effects reverted once the treatment ceased. Only 2 out of 10 patients in the placebo group reported new or worsening symptoms, which in both cases were related to changes in the disease-modifying therapy and that were therefore not classified as adverse events. The association between memantine therapy and transient neurologic impairment prompted the early termination of the study in March 2008 due to the limitations in

Patients were orally administered 30 mg of memantine or a placebo daily, starting with a titration dose of 10 mg per day and increasing by 10 mg each week until the final dose was reached. We tested the dose of 30 mg/day rather than the approved dose for patients with Alzheimer disease of 20 mg/day based on the good tolerance in patients with MS previously reported. Any change or discontinuation of the treatment was introduced by gradually decreasing the dosage by 10 mg each week. The primary endpoint involved assessing the efficacy of memantine in improving verbal memory performance using Buschke Selective Reminding Test. Secondary endpoints included the effects of memantine on 1) other cognitive domains such as attention (Symbol Digit Modalit Test, Stroop test) and executive performance (Raven’s Progressive Matrices, Paced Auditory Serial Addition Task); 2) quality of life (Short Form-36 scale); 3) disability (Expanded Disability Status Scale [EDSS]) and MS Functional Composite [MSFC]); 4) fatigue (MFIS-5 scale); and 5) safety. The study was designed as a 12-month crossover trial (6 months in each arm) and it planned to recruit 60 patients according to the following inclusion criteria: 1) patients with MS; 2) age between 18 and 65 years; 3) any MS subtype; 4) not having suffered a relapse in the last month; 5) moderate cognitive impairment defined as performing 1.5 SD below the control group (matched by age and education) in two or more neuropsychological subs tests of the Brief Repeatable Battery-Neuropsychology (BRB-N) as described previously. The use of disease-modifying drugs (interferon-beta, glatiramer acetate, or natalizumab) was permitted. Likewise, symptomatic therapy was also allowed but it had to remain unchanged for the month prior to inclusion and during the study. The exclusion criteria were as follows: 1) indications of psychiatric diseases (Cummings battery); 2) indications of depression (Hamilton scale ≥8); 3) drug or alcohol abuse; 4) benzodiazepine therapy or other medical diseases that might interfere with the study. A causal relationship between adverse events and medication was established using the Karch-Lasagna algorithm. Statistical analysis was performed by P.V. and G.A.

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maintaining the study blind, the high drop-off rate (six out of nine patients in the memantine arm), and the impairment of the patients’ quality of life.

**DISCUSSION** Our study indicates that intermediate to high doses of memantine might induce reversible neurologic impairment in patients with MS suffering moderate to severe physical disability. This impairment involves the functional systems frequently affected in patients with MS, such as the visual, motor, or cerebellar pathways. These events were reminiscent of pseudoexacerbation of MS due to fever, stressful events, or flu-like symptoms secondary to disease-modifying drugs, conditions that were ruled out in our patients. We classify these side effects as pseudoexacerbations rather than classic memantine side effects because they involved an impairment of previous symptoms, such as weakness of the limb in which the patient had experienced weakness previously. These effects do not appear at lower doses, below 20 mg/day, despite the mild escalation regimen (10 mg weekly escalation), and they disappeared shortly after reducing the dosage.

The biologic bases of such symptoms are unknown. The similarity of these pseudoexacerbations suggests that they might share a common mechanism, such as transient axonal blockage due to energy depletion of demyelinated axons.\(^{14}\) We hypothesize that the partial inhibition of overactive glutamatergic pathways by memantine coupled with the presence of demyelinated axons may contribute to produce transient axonal blockage. Memantine is a noncompetitive inhibitor of NMDA receptors, implying that the blocking effect is enhanced when glutamatergic pathways are more strongly activated,\(^{5}\) as associated with brain plasticity.\(^{15}\) The block of conduction in demyelinated axons seems to be secondary to the energy failure associated with ion channel and mitochondrial dysfunction.\(^{16}\) Other explanations might include direct synaptic blockage produced by memantine, its effects on serotoninergic, dopaminergic, and cholinergic pathways, or a direct effect of memantine on immune mediators, although there are no biologic data to support these hypotheses. The reversible nature of the effects of memantine on these neurologic symptoms does not suggest a direct effect of this drug on the excitotoxic damage to oligodendrocytes by glutamate.\(^{17}\) For this reason, better defining this phenomenon might improve our understanding of the pathophysiology of the neurologic symptoms in MS.

The patients in our study were moderately to severely disabled from both the cognitive and physical point of view. Thus, our cohort represents a subtype of patients with severe widespread brain damage who might be more susceptible to the side effects of me-

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**Table: Adverse events in the memantine trial in patients with multiple sclerosis**

<table>
<thead>
<tr>
<th>ID</th>
<th>Arm</th>
<th>MS subtype</th>
<th>EDSS</th>
<th>Disease duration, y</th>
<th>Symptoms</th>
<th>Severity</th>
<th>Action</th>
<th>Improvement after withdrawal of treatment</th>
<th>Causal relationship*</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Memantine</td>
<td>RR</td>
<td>3</td>
<td>21</td>
<td>Blurred vision</td>
<td>Mild</td>
<td>None</td>
<td>Yes</td>
<td>Drug adverse event</td>
<td>Possible</td>
</tr>
<tr>
<td>4</td>
<td>Memantine</td>
<td>SP</td>
<td>6</td>
<td>16</td>
<td>Increased muscle weakness, walking difficulties or unstable gait, and fatigue</td>
<td>Moderate</td>
<td>Stop medication</td>
<td>Yes</td>
<td>Drug adverse event</td>
<td>Probable</td>
</tr>
<tr>
<td>5</td>
<td>Memantine</td>
<td>RR</td>
<td>3.5</td>
<td>7</td>
<td>Increased muscle weakness, walking difficulties or unstable gait, and fatigue</td>
<td>Severe</td>
<td>Stop medication</td>
<td>No</td>
<td>Disease progression</td>
<td>Unrelated</td>
</tr>
<tr>
<td>6</td>
<td>Memantine</td>
<td>SP</td>
<td>6</td>
<td>11</td>
<td>Increased muscle weakness, walking difficulties or unstable gait, and fatigue</td>
<td>Mild</td>
<td>Stop medication</td>
<td>Yes</td>
<td>Drug adverse event</td>
<td>Probable</td>
</tr>
<tr>
<td>11</td>
<td>Memantine</td>
<td>PR</td>
<td>2.5</td>
<td>8</td>
<td>Severe headache and dizziness</td>
<td>Moderate</td>
<td>Stop medication</td>
<td>Yes</td>
<td>Drug adverse event</td>
<td>Probable</td>
</tr>
<tr>
<td>15</td>
<td>Memantine</td>
<td>RR</td>
<td>2</td>
<td>9</td>
<td>Increased muscle weakness and fatigue</td>
<td>Mild</td>
<td>Stop medication</td>
<td>No</td>
<td>Disease progression</td>
<td>Unrelated</td>
</tr>
<tr>
<td>17</td>
<td>Memantine</td>
<td>SP</td>
<td>7</td>
<td>7</td>
<td>Increased muscle weakness and fatigue</td>
<td>Moderate</td>
<td>Stop medication</td>
<td>Yes</td>
<td>Drug adverse event</td>
<td>Probable</td>
</tr>
<tr>
<td>22</td>
<td>Placebo</td>
<td>RR</td>
<td>4</td>
<td>4</td>
<td>Increased muscle weakness and fatigue</td>
<td>Mild</td>
<td>None</td>
<td>None</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

ID: identification number; MS: multiple sclerosis; Arm: treatment arm; EDSS: Expanded Disability Status Scale. *Causal relationship between adverse event and medication was established using the Karch-Lasagna algorithm.**

*EDSS = Expanded Disability Status Scale; RR = relapsing remitting; SP = secondary progressive; PR = progressive progressive; MS = multiple sclerosis.
mantine. However, a previous study with higher doses of mermantine (up to 60 mg/day) did not report such common side effects,6 even in highly disabled subjects. Nevertheless, the absence of blind clinical trials with mermantine in patients with MS may explain the failure to report such side effects. Finally, the fact that mermantine induces neurologic symptoms does mean it might not also improve cognition in MS or exert neuroprotective effects that might be beneficial against neurodegeneration in MS.5 Further studies are warranted to address this question.

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