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Memantine unproven to provide any clinical benefit in cases of vascular cognitive impairment

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ABSTRACT A critical appraisal and clinical application of Wilcock G, Möbius HJ, Stöffler A. A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). *Int Clin Psychopharmacol.* 2002 Nov;17(6):297-305. doi: 10.1097/00004850-200211000-00005.

Keywords: *Memantine, vascular dementia, vascular cognitive impairment*

Clinical Context

Our patient, a 60 year old woman, had suffered multiple ischemic cerebrovascular accidents in the past leaving her with left sided hemiplegia and bilateral blindness. She suffered from Chronic Kidney Disease (CKD), uncontrolled Diabetes Mellitus (DM), carotid artery stenosis, and hyperlipidemia. Although memory and cognition were not formally measured, the patient also suffered from impairments in both. This patient presented to our floor from a nursing home with severe dysphagia, requiring a Percutaneous Endoscopic Gastrostomy (PEG) tube. Her history of Cerebrovascular Accidents (CVA) left her a poor historian with little independence, unable to do most ADLs alone. The patient was severely distressed about going back to the nursing home. She wanted to live with her husband, despite his lack of training and equipment at home required to care for her. She didn't understand the extent of her disabilities and psychiatry deemed her lack of insight and judgment was due to cognitive impairments. Our patient was prescribed memantine 10mg daily while under our care.

Clinical Question

Does memantine clinically benefit patients suffering from vascular cognitive impairment?

Research Article

Wilcock G, Möbius HJ, Stöffler A. A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). *Int Clin Psychopharmacol.* 2002 Nov;17(6):297-305. doi: 10.1097/00004850-200211000-00005

Related Literature

I began my search on Pubmed with keywords such as "Memantine and Cognitive Impairment," resulting in research relating to Alzheimer's or patients with no specified etiology of dementia[1] and studies done on animal models. I refined my search by selecting "human" under filters and specifying my terms, such as "Randomized controlled trial," "double blinded," and "Memantine for

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treatment of Vascular Dementia." Results were narrowed to a few studies, one of which was a meta-analysis of randomized controlled trials studying the efficacy and adverse effects of cholinesterase inhibitors and Memantine in vascular dementia.[2] The conclusion of this meta-analysis showed small changes of uncertain clinical significance with these medications. The MMM500 trial claimed that memantine had a significant benefit on cognitive performance for patients with Vascular Dementia. This search found 168 citations on Memantine, of which only two trials were included. These same two trials were included in my primary search.[3,4] All other studies were either reviews (not clinical trials) or studies done on animal models, and therefore excluded from my search.

The MMM500 study is a 28-week, double blinded, randomized controlled trial of patients with mild to moderate vascular dementia who were given NMDA-antagonist, memantine, and compared with patients who were given the placebo. The MMM300 study was also a 28-week double blinded, parallel, randomized controlled trial with the same criteria. The difference between the two is the larger number of patients in the MMM500 trial (579), which is superior to the 321 participants in MMM300. Both trials shared the same methodology and findings were consistent between the two. Another double-blinded, placebo-controlled trial, "Efficacy and tolerability of memantine in patients with dementia syndrome," gave memantine vs placebo to 66 patients with vascular dementia.[5] This study was not seen as superior to the others because the patients were diagnosed with vascular dementia using Sandoz Clinical Assessment Geriatric Scale (SCAG), Syndrom-Kurz-Test (SKT), Mini Mental State Evaluation, and Tapping and Trace tests, while MMM500 trial used assessment tools more consistent with today's diagnostic criteria of vascular dementia, such as the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN), Diagnostic and Statistical Manual (DSM), Mini Mental State Examination (MMSE), and Computerized Tomography (CT)/Magnetic Resonance Imaging (MRI).[6]

Critical Appraisal

The MMM500 study was designed as a randomized, double-blinded, placebo-controlled trial. Outpatients were recruited in a consecutive manner at specialized geriatric centers by general practitioners and neurologists. Further information on the recruitment process of patients was not given. Whether patients themselves volunteered or were convinced by their physicians was not specified, but may play a role in participation bias. Inclusion criteria included the diagnosis of probable vascular dementia using DSM-III-R, NINDS-AIREN criteria, confirmed by Hachinski Ischemic Score of 4+, MMSE and CT/MRI imaging of the brain. The MMSE was used to assess the severity of vascular dementia (with a score between 10 and 22, corresponding to "mild-moderate" vascular dementia). The study excluded anyone with secondary causes of dementia, poorly controlled illnesses, psychotic episodes or on oral anticoagulants. While memantine administration is a feasible option for my patient of interest, this criteria excludes my patient who was on oral anticoagulants and had uncontrolled comorbidities such as CKD and DM.

Patients between the ages 54-97 received randomized study medication (284 patients allocated to placebo and 295 allocated to memantine). A balanced randomization was generated using SAS Statistical Software, by a statistician with no access to information on the people participating in the study. The demographic and baseline data of patients was evenly distributed. Patients, investigating staff and the Merz study team (suppliers of medication) were all blinded to treatment allocation. Primary efficacy parameters included ADAS-cog, a quantitative instrument designed to assess the severity of cognitive impairment and CGI-C (Clinical Global Impression scale), an interview conducted by the physician with the patient and their caregiver. Secondary efficacy parameters included the Gottfries-Brane-Steen Scale (GBS), an observer scale used to measure impairment of motor performance, intellectual capacity and emotional capacity; Nurses' Observation Scale for Geriatric Patients (NOSGER), which is used to assess memory, instrumental activities of daily living, mood, and social behavior; and MMSE. This study uses valid tools to assess patient progress, is completely blinded to all participants, and ensures randomization of patients. The tools used to assess efficacy/improvement also include measure outcomes that are important to patients and their caregivers. According to the SORT (Strength of Recommendation Taxonomy) this would be Level 2, based on a single, marginal quality study.[7]

A positive effect of the drug was defined as any positive change from baseline in the ADAS-cog and the Clinical Global Impressions Scale(CGI-C) score. The investigators used the ADAS-cog inappropriately, as a 4-point difference has been determined to be clinically meaningful.[8] At the end of the 28-week trial, 464 patients had completed it (226 on placebo and 238 on memantine). In the intention to treat (ITT) sample, the two arms of study differed by a mean of 1.75 points in the ADAS-cog scores from baseline, favoring Memantine (p-value < 0.0038). This is a statistical difference that is clinically meaningless, leading the investigators to

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misinterpret their own data. Thus, the results of this trial were actually consistent with the meta-analysis[2] showing benefit of doubtful clinical significance.

While both groups were assessed at baseline and throughout the trial an equal number of times, it's hard to say that all patients were treated equally. These outpatients received care from homes or family, which is difficult to standardize. For example, the drugs were split into 10mg b.i.d. While some patients may have received their full dose every day, others may have had an inconsistent medication schedule. As there is no definite treatment for vascular dementia, there was no gold standard to compare test results to.

Clinical Application

The decision to place my patient on memantine was not a well thought out decision. We did not assess her cognitive function with tools used in the studies (MMSE). The team agreed that they had read a few studies showing clinical improvement of vascular dementia patients and felt as though this patient, who had suffered from multiple previous CVAs leaving her severely impaired, had nothing to lose by trying this medication. Although multiple studies have demonstrated tolerance and safety of usage of memantine, this was still a clinical error, as our team did not delve deeper into the research we used to make our decision. No study has shown an ADAS-cog score difference of 4 or more, which has been shown to be necessary to notice clinical significance in patients with vascular dementia.[8] Therefore, despite any improvement in my patient's potential ADAS-cog score or CGI-C score, it is unlikely that this would have improved her quality of life. Also, despite the treatment being well tolerated, these studies eliminated patients taking psychotropic drugs, drugs with psychiatric side-effects, oral anticoagulants, and benzodiazepines. It has not been determined whether this drug is safe to take along with a list of other medications, and therefore it may not have been safe to use in my patient's case.

Learning points:

1. There is little research dedicated to memantine and its benefits in vascular dementia and there is great need for more research that delves deeper into subtypes of vascular dementia and how memantine benefits these different subtypes.

2. It is not enough to accept the definitions of "positive effects of a drug" that research publications give in their reports. It is necessary to take the extra step to define this based on research and evidence, and to critically appraise the results of these studies before clinically applying them to patients. I will carry this lesson with me throughout my career as a physician.

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