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An 8-week open label trial of L-Threonic Acid Magnesium Salt in patients with mild to moderate dementia

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ABSTRACT

Emerging research on the effects of a novel magnesium compound of L-Threonic Acid Magnesium Salt (L-TAMS) containing Vitamins C and D on cognitive performance suggests that supplementation may be of benefit to individuals with Alzheimer's disease (AD). The current open label trial explored L-TAMS effects in patients with mild to moderate probable AD. Fifteen patients with a clinical diagnosis of mild-to-moderate AD underwent 18F-FDG-PET imaging and neuropsychological testing, and blood draws at baseline and after 8 weeks of treatment in order to assess the acute effects of L-TAMS supplementation on cerebral glucose metabolism and cognitive performance. Neuropsychological testing and blood chemistries were also performed after 4 months of L-TAMS discontinuation. We did not find metabolic changes in *apriori* ROIs associated with AD rather, exploratory analyses showed statistical brain maps of cerebral-to-whole brain increases in regions not associated with AD. However, these findings were uncorrected for multiple comparisons and none of the findings survived multiple region comparisons. Although this study was underpowered to detect cognitive changes, a significant increase was found in MMSE scores after 8 weeks of L-TAMS treatment. No significant changes were found on other cognitive measures. The results of this study need to be interpreted with caution given significant study limitations including possible Type I error due to multiple comparisons, no comparison placebo group, and small sample size. Larger and longer, randomized placebo-controlled trials are needed to clarify whether L-TAMS treatment has significant effects on cognitive or relevant biomarkers in persons affected by or at risk for AD.

Introduction

In the United States, there are an estimated 5.2 million cases of Alzheimer's Disease (AD), with AD and other dementias affecting nearly 1 in 3 senior adults [2]. With the mounting financial and emotional toll of care for AD patients, the issue of finding safe and efficacious treatments is ever more pressing. Given the personal and global impact of AD, there is an urgent need for adjunctive or stand-alone treatments aimed at improving the long-term cognitive and functional outcomes by slowing or possibly halting the trajectory of cognitive decline.

Currently, persons with a clinical diagnosis of AD have few therapeutic options and those that are available, show only moderate efficacy in slowing cognitive changes [3–5], marginal clinical improvements [6,7], or temporary functional stabilization [8]. Cholinesterase inhibitors, the most common being donepezil, have been developed as an important and common treatment for people with AD. *N*-methyl-D-aspartate receptor (NMDA) antagonists such as memantine are also commonly used alone or combined with a cholinesterase inhibitor for treatment of AD. Results of treatment with NMDA receptor antagonists are shown to be similar to those of cholinesterase inhibitors [9]. However, neither cholinesterase inhibitors nor NMDA receptor antagonists halt disease progression.

Although data is limited, emerging research on a novel magnesium compound, L-Threonic Acid Magnesium Salt (l-TAMS), suggests that l-TAMS supplementation may have cognitive benefits in patients with AD [1,10–12] or normal elderly with subjective cognitive complaints [13]. The neurobiological effects of l-TAMS treatment have been studied in several studies using AD-like

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animal models [14,15] with findings that suggests a greater bioavailability of l-TAMS in the brain compared to non-significant increases with other magnesium compounds (i.e. magnesium citrate, magnesium chloride).

The current study was an open label, 8-week, proof-of-concept trial to assess whether supplementation with a combination regimen of instant release and sustained release tablets containing l-TAMS resulted in increased cerebral glucose metabolism in regions that are preferentially and progressively affected by AD, measured by 18F-FDG-PET, in patients with a clinical diagnosis of mild to moderate probable AD.

Specifically, we were interested in metabolic changes in regions predominantly affected in AD including the prefrontal cortex, parietotemporal cortex, and posterior cingulate cortex [16]. We also included the medial temporal cortex (including the hippocampus and entorhinal cortex) as a region affected in conversion to AD [17]. In addition to 18F-FDG-PET, we assessed measures of global cognitive functioning and the selected cognitive functions of attention, memory, semantic fluency, visuospatial abilities, and executive functions.

Materials and methods

Subjects

Subjects were recruited through local medical doctor referrals, fliers placed at Stanford clinics and the surrounding community, advertisements in local newspapers, clinical trials registries, and the Alzheimer's Association online clinical trials matching service.

Inclusion criteria included adults of either gender > 60 years of age (women had to be post-menopausal), a diagnosis of probable AD from their physician, a Mini-Mental State Examination (MMSE) between 14 and 24, adequate visual and auditory acuity to allow for neuropsychological testing, at least 12 years of education (or a GED to allow consistency of the sample), and willingness to or having a representative willing to sign the informed consent prior to enrollment into the study (for those subjects unable to sign or understand informed consent, assent to participate in the study was required), and agreeing to discontinue vitamins, minerals, or dietary/herbal supplements for at least 7 days prior to study entry and until after study completion.

Exclusion criteria included having one or more of the following medical conditions: Active heart disease, uncontrolled high blood pressure ($\geq$140/90 mmHg), hepatic or renal dysfunction as evidenced by ALT, AST, AP being $\geq$2 times the upper limit of normal or serum creatinine value $\geq$2.0 mg/dl or other clinically significant abnormal clinical laboratory value per primary investigator (PI) discretion, type I diabetes, unstable thyroid disease, unstable psychiatric illness or psychiatric hospitalization within the past year or, history of drug or alcohol abuse, immune disorder (such as HIV/AIDS), history of TIAs, carotid bruits, verified lacunes, significant pulmonary disease, history of cancer (except localized skin cancer without metastases or in situ cervical cancer) within 5 years prior to screening, or any medical condition or abnormality that, in the opinion of the PI would compromise the safety of the subject or the quality of the study data. Subjects were also excluded if they had participated in another research study within 30 days prior to the screening visit or had any contraindication for PET imaging including those unable or unwilling to lie down for 1 h.

Further exclusion criteria included use of any medications that are known to interact with magnesium including potassium-sparing diuretics because they could increase magnesium levels, loop and thiazide diuretics because they could decrease magnesium levels, muscle relaxants, chelating agents, anticholinergic medications, narcotics, antipsychotics, Parkinsonian medications, anticonvulsants, corticosteroids, anticoagulants, glutamate blockers (including memantine), use of an unstable dose of medication (defined as fewer than 90 days at the same dose), magnesium containing antacids, supplemental magnesium or any magnesium containing products, use of all dietary or herbal supplements or products including those purported to improve memory, improve sleep or decrease stress, having an allergy or sensitivity to any ingredient in the test product, or use of any medication deemed exclusionary by PI. Because the study product could reduce the absorption of antibiotics a washout period of 2 weeks was required for study participation. The PI evaluated any subject using calcium channel blockers. Although as needed benzodiazepine use was allowed, regular benzodiazepine use was not allowed during study participation. Use of cholinesterase inhibitors was not an exclusion criterion for this study.

Procedures

This was an open label trial of l-Threonic acid Magnesium containing Vitamin C and Vitamin D. While l-TAMS has been sold as a commercial supplement and is on the FDA Generally Recognized as Safe (GRAS) list, it has not been optimized for individuals with AD. The dosing schedule and formulations in this trial were designed specifically for AD patients. The daily dosage of l-TAMS was 1800 mg as follows: 1) 600 mg of 6-h sustained release l-TAMS (clinical code MMFS-201) in the morning and 2) one MMFS-201 tablet and one 600 mg instant release tablet (clinical code MMFS-101) in the evening. It is suggested that this sustained release formulation (MMFS-201) may serve to maintain elevated levels of l-TAMS in the periphery.

Subjects underwent 18F-FDG-PET imaging, neuropsychological testing, and blood draws for clinical data at baseline (Time 1; T1) and 8 weeks of MMFS-201-101 treatment (Time 2; T2). Neuropsychological testing was repeated 4 months after discontinuation of MMFS-201-101 treatment (Time 3; T3).

Clinical laboratory tests

Blood draws were conducted prior to treatment initiation to assess kidney and liver function, complete blood count, fasting plasma insulin, and red blood cell magnesium.

Neuropsychological testing

Neuropsychological testing was performed by study personal with expertise in the administration of neuropsychological measures. The following measures were utilized:

Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-COG; [19]). This is a widely used cognitive measure of global abilities in clinical trials of AD and used with permission from the NIA Alzheimer's Disease Cooperative Study (NIA Grant AG10483).

Delis-Kaplan Executive Function System (D-KEFS; [20]). This is a standardized battery that assesses higher order abilities (executive functioning). Two selected subtests were utilized.

Color-Word Test. This test is comprised of 4 subtests including Color Naming, Word Reading, Inhibition, and Inhibition/Switching.

Trail Making Test. This is a graphomotor test comprised of 5 conditions including Visual Scanning, Number Sequencing, Letter Sequencing, Number Letter Switching, and Motor Speed. Condition 4 (Number Letter Switching) is a measure of cognitive flexibility.

Mini Mental Status Examination (MMSE; [21]). This is a brief global measure of cognitive functioning.

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