

LETTERS

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Levetiracetam for agitated Alzheimer's disease patients

Based on the fMRI finding that increased cortical recruitment occurs in response to cognitive challenge in Alzheimer's disease (AD) (Johnson *et al.*, 2000), a CNS anti-kindling agent such as levetiracetam might be useful for treating agitation. Used for partial seizures, it has few side effects, is not metabolized by the liver and has virtually no drug-drug interactions (Privitera, 2001).

We undertook a 4-week open-label study of levetiracetam for agitation in community-dwelling AD patients. Appropriate informed consent was obtained. The principal outcome measure was the Neuropsychiatric Inventory (NPI) total score. We also administered the Mini-mental State Examination (MMSE), the Texas Functional Living Scale (TFLS); (Cullum *et al.*, 2001), a measure of daily function, and the Quality of Life in Dementia Scale (QUALID); (Weiner *et al.*, 2000).

Enrollees scored at least 10 points on the NPI and had at least a two-week history of two or more behaviors on the Agitated Behavior in Dementia Scale (Logsdon *et al.*, 1999), occurring at least once weekly, and caregiver-rated as at least moderately distressing. Patients were on stable doses of psychotropic drugs and/or cognitive enhancers; live-in caregivers administered levetiracetam. Dosage began at 500 mg bid and increased as clinically indicated at seven days to 500 mg qam and 1000 mg hs and at 14 days to 1000 mg bid. Dosage was decreased by 500 mg per day as indicated for adverse effects. Lorazepam 1 mg po qd for agitation or zolpidem 10 mg hs po for sleep were allowed.

Two data analyses were performed: first analyses included data using baseline and a second visit after baseline (last observation carried forward; LOCF). The second analyses included patients with both baseline and 4th week visits. Paired samples t-tests compared each patient's data on the two visits for the continuously measured variables. Difference scores were calculated as change from baseline (baseline – last measurement). Assumptions of the tests were examined for violations. SPSS V12.0 was used for analyses and significance was set at $p < 0.05$.

Of the 20 subjects enrolled (11 men and 9 women, average age = 70, range = 56–86 years), 13 had 4 week data. Of the 19 who received an initial dose, 12 reached 1500 mg qd at week 1 and 9, 2000 mg qd at week 2; of these, 8 were at 2000 mg qd at 4 weeks. Dosage was reduced in 2 persons because of lethargy and, in 1 person, increased agitation. Of the six early terminators (all on 500 mg bid), one dropped after the initial dosing visit, one experienced lethargy, one refused medication, one received disallowed medications, and one

was admitted to a locked facility due to inappropriate aggression. Two subjects became more agitated; one, more depressed.

There were small but significant post-treatment reductions for mean total MMSE scores 12.7 to 11.8; ($p < 0.05$) and total NPI scores 38.8 to 27.4; ($p < 0.01$) based on LOCF, with similar results for the completers (Total MMSE, $p < 0.05$; Total NPI, $p = 0.03$), and the delusions subscale of the NPI ($p = 0.03$) (see Table 1 published online at www.journals.cambridge.org/jid_IPG).

The median levetiracetam dose for completers was 2000 mg qd (range = 625–2000 mg). Side-effects included lethargy/fatigue (5), increased agitation/irritability (4), dizziness (2), decreased appetite (1), diarrhea (1), insomnia (1), and vivid dreams (1). Of the 19 who received at least one dose, 12 were receiving 1–3 psychotropic drugs, including SSRIs (6), lorazepam (5), trazodone (2), and neuroleptics (4). Of the five persons who received study drug alone; one had increased agitation and one developed lethargy.

In summary, we found frequent side-effects and possibly impaired cognition without great therapeutic efficacy. About six months after study completion, a patient who had continued on levetiracetam 500 mg bid suffered a generalized seizure following abrupt drug cessation, suggesting that if used, the drug should be withdrawn gradually.

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The transcobalamin 776C>G polymorphism may be a modifiable genetic risk factor for Alzheimer's disease

Accumulating evidence suggest that low vitamin B₁₂ status is associated with an increased risk of Alzheimer's disease (AD) (Refsum and Smith, 2003). Transcobalamin (TC) binds vitamin B₁₂ (cobalamin) in plasma and is the critical transporter that delivers vitamin B₁₂ to peripheral tissues and the brain. Polyacrylamide gel electrophoresis reveals two common isotypes of TC, M and X, and also two rare variants, S and F. The main genetic determinant of this phenotypic variability is a C-to-G transition at position 776 in relation to the first nucleotide (+1) of the ATG-translation initiation codon in the TC gene, which leads to a substitution of arginine for proline at amino acid 259 of TC (Zetterberg *et al.*, 2003a). The vast majority of individuals with the wild-type homozygous 776CC genotype (proline/proline) have the TC M phenotype, while most 776GG (arginine/arginine) individuals have the X phenotype.

We have shown that the TC 776G allele is strongly associated with lower levels of holo-TC (the vitamin B₁₂-TC complex) in cerebrospinal fluid (CSF) in patients with AD, in spite of normal vitamin levels in peripheral blood (Zetterberg *et al.*, 2003b). This indicates that holo-TC encoded by the 776G allele might cross the blood-brain barrier less efficiently or be less stable in CSF and, hence, less efficient with regards to delivering vitamin B₁₂ to the brain than 776C-encoded holo-TC. Moreover, we recently showed that the 776G allele is associated with earlier age of onset of AD (McCaddon *et al.*, 2004). Taken together, these findings suggest that improving the vitamin B₁₂ status of the elderly population by supplementation might postpone the development of AD in TC 776G homozygous and heterozygous individuals. It is, however, unknown if oral vitamin B₁₂ treatment improves the B₁₂ status in the central nervous system of these genotype carriers. Here, we determine the effect of oral vitamin B₁₂ treatment on holo-TC concentration in CSF in AD patients carrying the 776G allele.

Among outpatients being evaluated for cognitive dysfunction at the Neuropsychiatric Clinic, Malmö University Hospital, we selected 29 individuals (7 men, 22 women) who were on long-term oral vitamin B₁₂ treatment (1 mg daily). All underwent a thorough clinical examination and fulfilled the DSM-IV criteria for primary degenerative dementia of Alzheimer-type and NINCDS-ADRDA criteria for probable AD. The patients' mean age at disease onset (SD) was 75 (7.5) years. The study was approved by the Ethics Committee at the Malmö University Hospital and written informed consent was obtained from all patients or their closest relatives if a patient could not give valid consent.

Genotyping of the TC 776C>G polymorphism was performed using a solid-phase minisequencing technique (Zetterberg *et al.*, 2003b). Plasma total

vitamin B₁₂ was determined by a commercial method (Bayer Corporation) on a Beckman-Coulter instrument. CSF holo-TC was analyzed in parallel with the previously reported measurements of holo-TC in patients without B₁₂ treatment by ELISA (Zetterberg *et al.*, 2003b; Nexo *et al.*, 2002). Analytical imprecision was <10%.

As expected, median vitamin B₁₂ concentration (range) among the 29 vitamin B₁₂-treated patients was high, 639 (129–1480) pmol/L. Only three of these individuals had the wild-type homozygous TC 776CC genotype (10%). Nineteen individuals (66%) had the heterozygous 776CG genotype and seven (24%) had the homozygous 776GG genotype. Median holo-TC concentration (range) in CSF was 60.0 (57.0–66.0) pmol/L in individuals with the 776CC genotype, 63.0 (18.0–162) pmol/L in individuals with the 776CG genotype and 48.0 (24.0–138) pmol/L in individuals with the 776GG genotype. These concentrations are well above the previously reported levels found in wild-type homozygous (776CC) individuals without oral vitamin B₁₂ treatment [30.0 (12.0–54.0) pmol/L] (Zetterberg *et al.*, 2003b). There was no detectable negative influence of the 776G allele on holo-TC concentration, although a slight effect of the 776G-allele may have been missed due to the restricted sample size. Nevertheless, these data show that oral vitamin B₁₂ treatment is associated with higher overall levels of holo-TC concentration in CSF also in individuals with the hypotranscobalaminemia-associated TC 776CG and 776GG genotypes.

In conclusion, the TC 776C>G polymorphism seems to be a modifiable genetic risk factor for vitamin B₁₂ deficiency in the brain. Since the 776G allele is associated with earlier age of onset of AD (McCaddon *et al.*, 2004), our results warrant additional investigations addressing whether it is possible to delay the development of AD in individuals with 776CG and 776GG genotypes by high-dose oral vitamin B₁₂ supplementation.

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