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The Effects of Levetiracetam on Alcohol Consumption in Alcohol-Dependent Subjects: An Open Label Study

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Abstract

The aim of this open-label pilot study was to assess the efficacy and safety of the novel anticonvulsant agent, levetiracetam, for the treatment of alcohol dependence. A maximal dose of 2000 mg was administered daily for 10 weeks to alcohol dependent subjects ($n = 20$). Mean reported ethanol intake declined significantly from 5.3 to 1.7 standard drinks per day. Levetiracetam was well tolerated by most subjects.

Keywords

Alcoholism; anticonvulsant; pyrrolidine

INTRODUCTION

Levetiracetam is a novel antiepileptic medication approved as an adjunctive agent for treatment of partial onset seizures. Findings from several behavioral and pharmacological studies indicate that levetiracetam may be a useful medication for the treatment of alcohol dependence. It may block ethanol seeking behavior by inhibiting α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (1, 2). It may help to reduce excitability associated with alcohol withdrawal by attenuating the negative allosteric effects of zinc and β -carboline on brain GABA_A and glycine receptors (3). Levetiracetam administration decreased symptoms associated with alcohol withdrawal (4). Animal studies demonstrated reduction of the symptoms of chlordiazepoxide withdrawal (5). Preliminary clinical studies also indicated effectiveness in anxiety disorders (6–8).

In the present open-label clinical trial, the effects of levetiracetam treatment on alcohol consumption by alcohol dependent subjects was assessed. The dose of levetiracetam selected for use in this study was the same as the maximal dose used to treat alcohol withdrawal by other investigators (4).

METHODS

This was a 13 week-long open label trial with 1 week of screening, 10 weeks of treatment, and 2 weeks taper, with a final assessment in Week 13. It was approved by the Institutional Review Board of the Boston University Medical Center. Subjects provided written informed consent prior to screening. Subjects were men and women, ages 21 to 60 years, who met criteria for a DSM-IV TR (9) diagnosis of Alcohol Dependence assessed using the Structured Clinical Interview (SCID) (10). Subjects had minimal weekly alcohol consumption levels of 21 standard drinks for men and 14 for women over a 28 day-long consecutive period during the 90 day prior to screening, and had a score of 8 or higher on the Alcohol Use Disorder Identification test (AUDIT) (11). They were not dependent or abusing substances other than caffeine, ethanol, or nicotine and had negative urine toxicology results.

Exclusion criteria included: treatment with disulfiram, naltrexone, lithium, antipsychotics, anticonvulsants, and antianxiety agents or history of complicated withdrawal from alcohol.

Levetiracetam was titrated up to a 1000 mg twice daily over the first three weeks of the study to a total of 2000 mg. The dose could be lowered if necessary based on adverse effects. Weekly counseling sessions were also provided using BRENDA guidelines (12).

Alcohol withdrawal was monitored using the Clinical Institute Withdrawal Assessment for Alcohol-Alcohol Revised (CIWA) (13). The intensity of craving for alcohol was measured with the Obsessive Compulsive Drinking Scale (OCDS) (14). Measures of efficacy included the Clinical Global Impression scales (CGI), clinician and subject rated scales, the Timeline Follow Back (TLFB) (15), the Addiction Severity Index-Lite (ASI-Lite) (16), Profile of Mood States (POMS) (17), and the Medical Outcomes Sleep Scale (MOS) (18). Anxiety and depression were assessed using the Hamilton-Anxiety (HAM-A) (19) and the Hamilton-Depression (HAM-D) scales (20), respectively.

Data Analysis

Baseline alcohol consumption was determined by taking the mean drinks consumed per day for the period between screening and the start of treatment using the TLFB. Baseline for other measures was taken to be the last score obtained prior to the start of treatment. Thus, baseline measures for TLFB and other measures reflect occurrences from overlapping time periods.

An intent-to-treat analysis of the primary outcome measure, mean daily drinks consumed for baseline and each treatment week was conducted. Subjects were evaluable if they completed 2 or more weeks of the treatment phase and consumed alcohol during the baseline phase.

Assessment measures obtained during baseline and treatment phase were compared using a repeated measures mixed models analysis approach (Proc Mixed, SAS version 9.1) (21). Separate comparisons were performed for baseline and Week 13 assessments. Least mean squares between baseline and treatment week assessment data were compared using t-tests with Dunnett-HSU adjustment of p values.

RESULTS

Twenty subjects were randomized into this study. Thirteen subjects completed the full maintenance dose phase of the study through Week 10. Eleven subjects completed the taper down to a total of 12 weeks on medication. The evaluable subject group includes sixteen subjects, 12 males and 4 females. The mean maximal dose administered to the evaluable subjects was 1781 (SD $\pm$ 407) mg. Fifteen of these subjects were white and one African American. Their mean age was 50.7 (SD $\pm$ 8.7) years and they had completed a mean of 15.4 (SD $\pm$ 2.3) years of education. Mean CIWA scores for subjects were low 2.8 (SE $\pm$.6) at baseline and remained so to the end of maintenance treatment phase. In the intent to treat analysis, the time effect for mean daily drinks consumed during the baseline period and for each of the first 10 treatment weeks was significant [$F(10, 134) = 2.75$; $p = .004$]. The time effect for the evaluable subjects was also significant (see Figure 1) [$F(10,130) = 3.44$; $p = .0005$]. Also, consistent with an improvement in these subjects' alcohol use problems were significant declines in the Alcohol composite score of the ASI-Lite from a mean of .54 (SE $\pm$.04) for the baseline period to .35 (SE $\pm$.05) [$F(1, 14) = 10.0$; $p = .007$] for Week 6 and .27 (SE $\pm$.05) [$F(2,23.1) = 9.7$; $p = .0009$] for the follow-up visit. No significant changes were detected for any of the other composite scores determined for the ASI-Lite. Finally, alcohol craving as assessed using the mean total OCDS scores, also declined significantly from baseline [21.7 (SD $\pm$ 9.4) during weeks 4 [13.8 (SD $\pm$ 8.00)] and 8 [12.9 (SD $\pm$ 9.4)].

Ratings by both the clinicians and subjects on the CGI scales indicated a significant improvement in subjects from the baseline through Week 10 and Week 13. At baseline, the mean CGI-Clinician rated scores were 4.1 (SE $\pm$.2), while for Week 10 and Week 13 scores were 1.9 (SE $\pm$.3) and 2.1 (SE $\pm$.4), respectively. For the subject rated CGI scores, mean scores were 3.4 (SE $\pm$.2) for the baseline period, 1.5 (SE $\pm$.3) for Week 10, and 1.4 (SE $\pm$.4) for Week 13.

The only significant change from baseline levels on the subscales of the POMS was an elevation in the mean Fatigue subscale score for Week 6 [$F(1, 10.9) = 65$; $p = .03$] from 3.9 (SD $\pm$ 4.4) to 6.8 (SD $\pm$ 5.1). No significant changes from baseline in any measures of sleep quality as assessed using the MOS were found.

Mean baseline HAM-A and HAM-D scale scores were 5.4 (SE $\pm$ 1.1) and 6.2 (SE $\pm$.95), respectively, indicating no anxiety or depression. The time effect for the baseline and treatment periods was significant for the HAM-A scores [$F(5,56.2) = 3.3$; $p = .01$], but this reflected only modest declines over the treatment period which were not clinically significant [the mean score for week 10 HAM-A was 2.3 (SE $\pm$.6)]. There was no significant difference between HAM-D scores at baseline and at Week 10.

Two subjects experienced irritability and one subject was sedated during treatment with levetiracetam. Several adverse events occurred in the case of a fourth subject. These included a prickly sensation, exhaustion, indigestion, feeling spacey, and vomiting. The proportion of subjects who stated in response to question P7 of the ASI-Lite that they "experienced trouble understanding, concentrating, or remembering" between the baseline (.3, SE $\pm$.11) and Week 6 (.08, SE $\pm$.1) decreased at a level that approached significance [p

= .08]. Ratings of concentration and memory as assessed by question 5 of the HAM-A did not differ significantly between the mean value obtained at baseline (.5, SE $\pm$.2) and any of the mean values obtained during either the treatment or the Week 13 visits.

DISCUSSION

A group of actively drinking alcohol-dependent individuals either significantly reduced their drinking or achieved abstinence with levetiracetam treatment. Reductions in the mean total OCDS, ASI Alcohol Composite scores, and the CGI scores suggest that levetiracetam may be effective for the treatment of alcohol dependence.

These findings add to growing evidence that anticonvulsants may have efficacy in the treatment of alcohol dependence, as shown in studies of carbamazepine (22), oxcarbazepine (23), valproate (24, 25), and topiramate (26, 27). Anticonvulsants offer a novel approach to alcoholism treatment because they can be given to actively drinking individuals. They may help patients who are attempting to stop drinking through suppression of the onset of symptoms of alcohol withdrawal. CIWA scores, for example, were low at the start of the study while many subjects were still actively drinking, and remained low, most likely as a result of treatment with levetiracetam. Anticonvulsants have also been used in relapse prevention, and identifying a medication that is effective both in treating alcohol withdrawal symptoms and preventing relapse to drinking would be a major advance in the pharmacotherapy of alcoholism.

Levetiracetam did not impair cognition based on the HAM-A and ASI components that evaluate memory and concentration, which may be an advantage compared to other anticonvulsants, such as topiramate, that are associated with cognitive disturbances (28). The low incidence of reported adverse effects shows that the drug had good tolerability in the study population.

Despite the open label design of the study, the findings provide evidence that levetiracetam can be safely administered to alcohol dependent patients and that it holds promise as a medication for the treatment of alcohol dependence at doses used for seizure disorders (29). Future double blind studies of levetiracetam are warranted.

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Figure 1.

The mean ($\pm$ S.E.) number of standard drinks consumed by evaluable subjects ($n = 16$) per day baseline period and treatment weeks 1 through 10.

*Indicates $p < 0.05$ for comparison with baseline values.