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LETTER TO THE EDITORS

Levetiracetam as monotherapy or add-on to valproate in the treatment of acute mania—a randomized open-label study

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Introduction

Anticonvulsants are a mainstay in the treatment of bipolar disorder. Valproate (VPA) and carbamazepine have been widely accepted in the treatment of acute mania and mixed states. There is evidence that while combination treatment of VPA or lithium with other anticonvulsants or atypical neuroleptics improves manic symptoms better than monotherapy, it also increases the risk of side effects that often lead to treatment discontinuation (Smith et al. 2007; Lin et al. 2006). Thus, new adjunctive treatments with well-tolerated effective drugs are required. Levetiracetam (LEV) is a new antiepileptic drug providing wide clinical efficacy in partial and in generalized epilepsy (Ben-Menachem and Gilland 2003). The mechanism of its action is not completely known so far but might include an atypical GABAergic effect (Patsalos 2000). To further define the clinical profile of LEV, we conducted a randomized, open trial in manic patients treated either with VPA monotherapy or with adjunctive LEV over a period of 10 weeks.

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Materials and methods

Thirty patients met the Diagnostic and Statistical Manual of Mental Disorders IV criteria for mania. The Study inclusion criterion for patients was a Young Mania Rating Scale (YMRS) score greater than 20, where the cutoff level was a YMRS score greater than or equal to 40. Patients were not included if they had one or more comorbid axis I or axis II diagnoses other than bipolar I disorder. All patients gave oral and written informed consent approved by the local Ethics Committee. Patients were randomized to either the monotherapy group with VPA or to the combination treatment group with VPA and LEV. Dose adjustment was based on clinical impression, rating scale scores, and plasma levels for VPA (50–120 mg/l) at each of the four visits. Maximum doses for LEV were set at 5,000 mg/day and for VPA at 3,000 mg/day or when plasma levels of 120 mg/l were achieved. Rescue medication included lorazepam up to 2 mg/day and zopiclone 7.5 mg/qhs. Patients were seen and rated weekly (visits 1 and 2), at week 5 (visit 3), and after further 5 weeks (visit 4) at the end of this study. At all visits, patients underwent the following rating scale scores: YMRS, Hamilton Depression Scale (HAM-D), Clinical Global Impression Scale for Bipolar Disorder (CGI-BP), and the Global Assessment of Functioning Scale (GAF). A positive response was operationalized as a 50% drop in YMRS rating and considered the primary outcome measure. Rating scale assessments and serum levels of both medications and, if necessary,

dose adjustments were performed at every visit. Dropouts were treated according to the intention-to-treat principle (last observation carried forward).

Results

Thirteen patients in the combination treatment group and 12 in the monotherapy group completed the study. Two patients dropped out within the first week of treatment for administrative reasons and an additional three after the second visit for lack of efficacy (two in the monotherapy group and one in the combination treatment group). Both groups were age and sex matched. Baseline scores for the rating scales were as follows: YMRS, 26±5 vs. 25±4; HAM-D, 4±2 vs. 4±0; GAF, 39±11 vs. 40±12; and CGI-BP, 5±1 vs.5±1. Thirty percent of patients in both groups were currently taking a mood stabilizer. The majority of patients had stopped their mood-stabilizing treatment prior to or at the time of onset of the manic episode. Patients in both groups had experienced similar numbers of previous episodes for depression (5.7 vs. 5.1) and for mania (3.9 vs. 4.3). The mean dose of study medication LEV was increased within a week to a mean dose of 2,500 (±641) mg/day. VPA was increased to a mean dosage of 1,232 (±324) mg/day in the monotherapy group and of 1,328 (±367) mg/day in the combination treatment group. There was no significant difference in VPA dose in either group. Combination treatment with LEV did not lead to a faster or better improvement of manic symptoms.

Response was calculated as a 50% reduction in YMRS scores at visit 4. The responder rates closely correspond with the YMRS drops in each group. They are as follows: no treatment effects were observed at visit 1 in either group. At visit 2, three subjects (25%) in the monotherapy and three (23%) in the combination therapy group responded. At visit 3, five monotherapy (45%) and five (38%) in the combination treatment had responded. At visit 4, an additional two subjects in the monotherapy and three in the combination treatment group had responded, equaling a total response rate for the former of 60% and for the latter of 62% (overall response rate=61%). There was no significant difference between the two groups. Remission (defined as a YMRS score less than or equal to 8) was reached by 50% of patients in the monotherapy group and by 54% in the combination treatment group. Again, there were no statistically relevant group differences observed. There were no statistically significant differences between the two treatment groups with respect to HAM-D (p=0.53), GAF (p=0.69), and CGI-BP (p=0.84) scores at visit 4. There was a significant difference ($p \leq 0.05$) with respect to side effects between the two groups: 46% of the patients in the combination treatment group suffered from side effects as opposed to 8% in the monotherapy group. Two (vs. one) complained about headache, one about dizziness, one about urinary incontinence, and one about weight increase. None of the patients dropped out due to side effects. Adjunctive medications such as lorazepam and zopiclone were required in both groups. LEV combination treatment did not lead to significantly lower doses of lorazepam (p=0.073) but to a significantly lower dose of zopiclone (p=0.024).

Discussion

This randomized open-label study was performed to further define the clinical profile of LEV. We compared adjunctive LEV to a standard treatment with VPA. Our results suggest that LEV does not lead to a better or faster improvement of manic symptoms when added to VPA. A total of 61% in both treatment groups responded, and 52% of the patients achieved remission. While this did not reach statistical significance, it suggested a trend toward better antimanic efficacy of the combination treatment. Patients receiving combination treatment had more side effects and required less sleeping medication. The open-label design and the small number of patients limit the generalizability of our results to other patient groups. However, all published work on LEV in bipolar disorder has similar limitations (Braunig and Kruger 2003; Kushner et al. 2006; Ghaemi et al. 1998). It should be noted though that this is the first randomized study on LEV in mania that extends over a period of 5 weeks. We cannot exclude that higher LEV and/or VPA doses would have added more benefit in this population.

While anticonvulsants are widely used in the treatment of bipolar disorder, several of these drugs with prominent actions on GABAergic mechanisms have recently been shown not to have potent acute antimanic efficacy. These include gabapentin and to some extent topiramate (Kushner et al. 2006; Ghaemi et al. 1998), all of which have been shown to increase brain γ-aminobutyric acid (GABA) in humans. LEV treatment leads to an indirect enhancement of benzodiazepine GABA receptor function by removing the negative modulation of this site by zinc and beta carbolines or other GABAergic mechanisms, which might explain why it is not as potent as other antimanic agents. However, this mechanism suggests the possible utility of further exploration of this drug in depression and in the prophylaxis of bipolar disorder. In conclusion, this randomized, open exploration of LEV as an adjunctive treatment in acute mania to a standard regimen of VPA did not identify any benefit of this drug to response or remission of manic symptoms. Regardless, it might be useful to perform studies using higher doses of LEV than employed in this trial. Furthermore, the pharmacological profile of LEV warrants

investigations of its antidepressant and prophylactic properties in bipolar disorder.

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