CASE REPORT
Levetiracetam for Acute Mania
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Abstract

Background: Treatment resistant of manic patients are a dilemma in psychiatry, In these cases, the clinician must consider the off-label use of newer psychothropics. Levetiracetam (LEV) is a novel anticonvulsant that is effective as antimanic in some case reports. This study aimed to assess the efficacy of LEV in the treatment of mania. Method: Three males with mania, resistant to regular treatments, received 500 mg of LEV titrated to 1500 mg/day as open, adjunctive treatment. Clinical response was assessed by Young Mania Rating Scale (YMRS), four weeks after drug administration. Results: All cases had symptom reduction, ranging from 37 to 10.6. None of the patients experienced adverse effects. Conclusion: We conclude that LEV appears to be a potentially useful drug in the treatment of acute mania (German J Psychiatry 2005; 9: 141-143).

Keywords: treatment, mania, levetiracetam, Young Mania Rating Scale

Introduction

Bipolar disorder prevalence is about 1.5% worldwide (Carta & Angst, 2005). This disorder is a debilitating illness characterised by extreme swings in mood, energy and functional ability. Effective and rapid control of acute mania is required to prevent potential harm to patients and their families. Most guidelines recommend antipsychotics, lithium, anticonvulsants (valproate and carbamazepine) and benzodiazepines as first line treatment of acute mania. For instance, the Expert Consensus Panel for Bipolar Disorder (Frances et al., 1996) recommended starting a monotherapy with a mood stabilizer for the acute phase of manic, mixed or hypomanic episodes and to add adjunctive antipsychotic or benzodiazepine medication only when psychotic features, agitation or insomnia are present. Similarly, the Expert Consensus Guideline for Medication Treatment of Bipolar Disorder (Sachs et al., 2000) considered use of a mood stabilizer alone as treatment of choice for a first manic episode, except in mania with psychotic symptoms where combination with an antipsychotic was preferred. The revised Practice Guideline for the Treatment of Patients with Bipolar Disorder, issued by the American Psychiatric Association in 2002, recommended initiation of either lithium plus an antipsychotic or valproate plus an antipsychotic as first-line treatment for more severe manic or mixed episodes. For less ill patients, monotherapy with lithium, valproate or an antipsychotic such as olanzapine was suggested if sufficient. The 2003 guidelines from the British Association for Psychopharmacology (Goodwin, 2003) recommended an antipsychotic or valproate for the initial treatment of a severe acute mania or mixed episode, with lithium or carbamazepine as further options for less ill patients. On the other hand, Grunze et al. (2002) recommended antipsychotics only as a third option, after unsuccessful change to a second mood stabilizer.

However, lack of response in some patients and unacceptable side effects causes continuing investigation for new drugs with more efficacy and better side effect profile.

Levetiracetam is a novel anticonvulsant approved for adjunctive treatment of partial seizures, which has no clinically significant drug interactions and has limited adverse effects (Leppick 2001). It offers the additional advantages of 100% bioavailability, lack of protein binding, and pure renal excretion (Loscher et al.1998). A specific mechanism of action for
this drug has not been characterized, however, in animal studies, LEV has shown potent anti-kindling properties (Lamberty et al. 2001). There are limited data for LEV treatment of patients with mania: In an animal model of mania Lamberty et al. reported good response with LEV (Lamberty et al. 2001). Goldberg and Burdick (2002) reported a case with 27 years history of non rapid cycling bipolar disorder that did not tolerate valproate and olanzapine because of sedation and nausea, treated successfully with LEV 2500 mg/day. Kaufman (2004) reported a case with resistant rapid cycling bipolar disorder who failed 15 psychotropic, individually or in various combinations, responded to LEV monotherapy and remained without bipolar features during one year of maintenance treatment. Because sufficient data about efficacy of LEV in acute mania is not available, this study can be one step forward in field of bipolar treatment. In this study we describe the effect of LEV on manic features in patients with refractory mania.

Table 1. Sample Characteristics

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age</th>
<th>YMRS Pre LEV</th>
<th>YMRS Post LEV</th>
<th>Improvement</th>
<th>Adverse effects</th>
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<tbody>
<tr>
<td>A.A</td>
<td>48</td>
<td>45</td>
<td>8</td>
<td>82.3%</td>
<td>None</td>
</tr>
<tr>
<td>H.B</td>
<td>35</td>
<td>38</td>
<td>19</td>
<td>50.0%</td>
<td>None</td>
</tr>
<tr>
<td>K.V</td>
<td>40</td>
<td>28</td>
<td>5</td>
<td>82.2%</td>
<td>None</td>
</tr>
<tr>
<td>Mean</td>
<td>41</td>
<td>37</td>
<td>10.6</td>
<td>71.5%</td>
<td>None</td>
</tr>
</tbody>
</table>

YMRS=Young Mania Rating Scale, LEV=Levetiracetam

Methods

Subjects of this study (3 cases) were the patients who admitted to the psychiatric ward with a diagnosis of Bipolar I Disorder, Manic Episode according to DSM IV TR criteria (one patient from the psychiatric ward of Rajaee Hospital, Yasuj University of Medical Sciences, Yasuj, Iran, from 22/5/2005 to 2/6/2005 and two patients from the Salman hospital, Yasuj from 3/7/2005 to 3/8/2005).

The trial was performed in accordance with the declaration of Helsinki and subsequent revisions and approved by the ethics committee of Yasuj University of Medical Sciences. Written informed consents were obtained before entering into the study from the guardians of the patients.

All cases received 500 mg of LEV titrated to a target dose of 1500 mg/day as open adjunctive treatment.

The Young Mania Rating Scale (YMRS) was used as measurement tool for assessing the treatment response (Young et al. 1978). The scale was performed at initiation and 4 weeks after treatment.

Results

Patients were ranging from 35 to 48 years (Table 1). All patients had failed multiple psychotropic agents. At the time of LEV initiation, patients had a mean YMRS score of 37 (ranging from 28 to 45). No patient had shown any considerable side effects following LEV treatment. After four weeks, the mean of the YMRS total score was 10.6 (ranging from 5 to 19).

Case I

A. A. is a 48 years old white man with a 17 years history of Bipolar I Disorder. He had no psychiatric comorbidities according to the Structured Clinical Interview for DSM IV TR (SCID). He had suffered from diabetes mellitus for 5 years that recently had been non-controlled despite treatment. Mr. A. had experienced his first manic episode at age 31 and had no depressive episode. He had 28 lifetime psychiatric hospitalizations and no history of suicidal attempt. His recent episode began 8 months ago with irritability, insomnia, restlessness, hypersexuality on the YMRS). Previous episodes had been modestly responsive to fluphenazine, clozapine, lamotrigine, chlorpromazine, pimozide and lithium, but this recent episode did not respond to clozapine (450 mg/24h orally) plus haloperidol (25 mg/24h intramuscular). LEV was prescribed to Mr. A at 500 mg/day and increased over 5 days to 1500 mg/day. His score on the YMRS decreased to 8 in the fourth week, then clozapine was tapered and his blood sugar decreased to normal range, while the patient did not experience any side effects.

Case II

H. B. is a 35 years old white man with 21 years history of bipolar I disorder. He has no psychiatric comorbidities according to structured clinical interview for DSM-IVTR. Mr. B. had experienced his first manic episode at age 14 and his first depressive episode at age 25. He had 41 lifetime psychiatric hospitalization and had an attempt to suicide at age 25. Recently he presents with 11 month history of elevated mood, pressured speech, sleeplessness and related symptoms (a baseline score of 38 according to YMRS). Previous episodes had been responsive to lamotrigine, lithium, sodium valproate, trifluoperazine, olanzapine, clozapine, risperidone and thioridazine. Six weeks trial of a mean dose of 15 mg/day of olanzapine (maximum dose was 25 mg/24 hours at sixth week), and 1200 mg/day of lithium (also, a mean dose of 20 mg/day of haloperidol intramuscularly were given to him by PRN order) was continued despite of any therapeutic response. LEV was prescribed to Mr. B at 500 mg/day and increased over 5 days to 1500 mg/day. His score on the YMRS decreased to 19 at 4th week, while the patient did not experience any side effects.
Case III

K.V. is a 40 years old white man with 17 years history of Bipolar I Disorder. He has no psychiatric comorbidities. He presented with elevated mood, pressured speech, sleeplessness and paranoid delusion (a baseline score of 28 on the YMRS). Mr. V. had experienced his first manic episode at age 23 and his first depressive episode at age 24. He had 15 lifetime psychiatric hospitalization and had no attempt to suicide. Previous episodes had been modestly responsive to lithium, risperidone, chlorpromazine, sodium valproate, thioridazine, clozapine, carbamazepine, perphenazine and trifluoperazine. A six weeks trial of 2000 mg/day valproate and a of trifluoperazine (mean dose of 15 mg/day; the maximum dose of trifluoperazine was 35mg/day orally in the sixth week) was continued despite of any therapeutic response. LEV was added to this regimen at 500 mg/day and increased over 5 days to 1500 mg/day. His score on the YMRS decreased to 5 at the 4th week and he experienced no considerable side effects.

Discussion

Antipsychotics, lithium, anticonvulsants (valproate and carbamazepine) and benzodiazepines are the first line treatment of acute mania, but lack of response in some patients and unacceptable side effects causes continuing investigation for new drugs with more efficacy and better side effect profile. Levetiracetam is a new antiepileptic drug, which received US Food and Drug Administration (FDA) approval in 1999 for adjunctive therapy of partial onset seizures (Leppik 2001).

This study aimed to expand the clinical experience with LEV as an antimanic drug. In our study LEV adjunctive therapy resulted in rapid reduction and total remission of bipolar features in all cases, and in one case (Mr. A.A) resulted in better diabetes mellitus control. Regarding the rule that we must have enough data about efficacy of a new drug for a disorder before performing extensive research, this study provides additional evidence in favour of efficacy of LEV in mania.

The efficacy of some antiepileptic drugs for treatment of mania, a unique inhibitory mechanism of LEV, and positive results of this study and other similar studies all suggest that LEV may be an effective antimanic drug with minimal side effects. Now, randomised controlled trials are needed to confirm the efficacy of LEV in treatment of acute mania.

Limitations of this study include the open-label design and lack of systematic drug level reports.

References


