Levetiracetam Induces a Rapid and Sustained Reduction of Generalized Spike-Wave and Clinical Absence

Jennifer Cavitt, MD; Michael Privitera, MD

Background: Levetiracetam (LEV) is a new antiepileptic drug with efficacy in partial-onset seizures. We report a case in which generalized-onset absence seizures responded clinically and electrographically to LEV.

Methods: We evaluated with continuous video/eleetroencephalography an adult with generalized-onset seizures given 3 antiepileptic drugs, 1 of which was LEV. Levetiracetam initiation 2 months before admission decreased patient-reported seizures. Interictal electroencephalography revealed generalized 3.5-Hz spike-wave and polyspike-wave discharges. Spike-wave bursts lasting 2 seconds or longer caused a pause in continuous reading aloud, consistent with clinical absence seizures. Levetiracetam was discontinued on admission, lamotrigine was gradually discontinued across 2 days, and topiramate was not changed. One encephalographer counted from video/electroencephalography recordings the number of spike-wave bursts in 1-hour time samples that included wake and sleep time.

Results: Spike-wave bursts increased from 4 to 56 per hour at baseline (4000 mg of LEV per day) to 406 to 914 per hour less than 48 hours after LEV discontinuation. Levetiracetam treatment was restarted, and 3 hours after the first dose of 1000 mg, spike-wave bursts dropped to 135 per hour. Response was sustained during the next 2 days.

Conclusions: This case showed a dramatic, rapid effect of LEV discontinuation and reinstitution on generalized spike-wave burst frequency and clinical absence. The effects were independent of reduction of lamotrigine and without change in topiramate doses and occurred in a time course consistent with LEV pharmacokinetics. Levetiracetam may be effective in generalized-onset epilepsy, and randomized, controlled trials are indicated.

Arch Neurol. 2004;61:1604-1607

EVETIRACETAM (LEV) IS AN antiepileptic drug approved in many countries for use in patients with partial-onset seizures. Although randomized, double-blind, controlled clinical trials have focused on patients with partial-onset epilepsy, preliminary evidence suggests LEV may also have an effect on primary generalized seizure types as well. Animal studies in genetic models of epilepsy and small open-label or single-blind trials in humans indicate LEV may reduce the frequency of generalized-onset seizures, but no randomized, controlled trials have studied this. In addition, there is little published information regarding the effect of LEV on epileptiform discharges on electroencephalography (EEG). We evaluated with video/EEG a patient with generalized absence-type seizures who showed a dramatic response of generalized spike-wave burst frequency and clinical absence to the discontinuation and then reinstitution of LEV.

Methods
A 34-year-old woman with medication-resistant seizures since early childhood was admitted to the Epilepsy Monitoring Unit at University of Cincinnati Hospital. She had a single, simple febrile seizure at age 18 months. Shortly after that, she began having frequent unprovoked generalized tonic-clonic-type seizures, as well as 2 other seizure types. Inpatient video/EEG monitoring at another epilepsy center in 1999 demonstrated generalized 4- to 5-Hz spike-wave discharges during clinical seizures, leading to the diagnosis of atypical juvenile myoclonic epilepsy. The patient described her typical seizures as being similar in character since early childhood. She reported that staring episodes lasting 3 to 7 seconds without postictal confusion were occurring 10 to 25 times per day, and generalized tonic-clonic seizures were occurring 4 times per month. The patient reported that once or twice a month she experienced staring spells lasting 20 seconds to 2 minutes with moaning and some postictal confusion.

Initiation of treatment with LEV and titration to 4000 mg per day 2 months prior to admission had resulted in a marked decrease in
patient-reported seizures. Treatment with lamotrigine (LTG) for more than 8 months prior to admission had produced a modest reduction in patient-reported seizures. On admission, her LTG dose was 600 mg/d with a level of 3.9 µg/mL. Topiramate (TPM) therapy, 150 mg/d, was already in the process of being slowly discontinued owing to intolerable adverse effects with doses of up to 400 mg/d. A previous trial of valproic acid years before had produced “the best” seizure control according to the patient, but it also caused intolerable nausea, vomiting, and diarrhea. Renal and hepatic function were normal. Interictal EEG showed generalized 3.5-Hz spike-wave and polyspike-wave discharges with bifrontal predominance; intermittent polymorphic delta activity was also seen over the left temporal region. Magnetic resonance imaging showed slightly decreased volume and slightly increased signal in the right hippocampus compared with the left, although several images were limited owing to motion artifact. Full scale IQ was in the borderline range.

The patient was monitored with continuous video/EEG from January 2, 2002, at 6 PM, to January 7, 2002, at 11 AM. Levetiracetam therapy was discontinued on admission (last dose, January 2, 2002, before 12 PM), LTG therapy was gradually discontinued across 2 days, and TPM therapy was not changed (Table).

### RESULTS

Spike-wave bursts occurred 4 to 56 times per hour during the first 36 hours. The frequency of spike-wave bursts increased to 406 to 914 per hour between 37 and 47 hours after LEV discontinuation (Figure 2). During this period, approximately 50% of the EEG findings were spike-wave bursts. The first dose of 1000 mg of LEV was given at 4 PM on January 4, 2002, and the EEG analysis at 7 PM showed 135 spike-wave bursts per hour. A continued decrease to 30 to 126 per hour was seen during the next 2 days, as the daily dose of LEV (but not LTG) was increased back to 100% of the baseline (maximum) dose. Just prior to discharge, a retrial of valproic acid was initiated, despite the history of intolerable adverse ef-

### Table. Preadmission and Postadmission Antiepileptic Drug Dosing by Hospital Day*  

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prior to Admission</th>
<th>Day 1</th>
<th>Day 2 (at 4 PM)</th>
<th>Day 3</th>
<th>Day 4 (at 6 PM)</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEV</td>
<td>4000</td>
<td>Discontinued upon admission (after 2000 mg morning dose at home)</td>
<td>1000</td>
<td>2000</td>
<td>3000</td>
<td>4000</td>
</tr>
<tr>
<td>LTG</td>
<td>400 (level = 3.9 µg/mL)</td>
<td>100 (at 9 AM, then discontinued)</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>TPM</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>VPA</td>
<td>NA</td>
<td>150</td>
<td>NA</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; LEV, levetiracetam; LTG, lamotrigine; TPM, topiramate; VPA, valproic acid.

*Data are presented as mg/d. Each hospital day represents a consecutive 24-hour period starting at 6 PM on January 2, 2002. Discharge on day 5, January 7, 2002, occurred at 11 AM.
fects with this medication, based on the history of best seizure control with valproic acid. At 1-month and 8-month follow-up visits on valproic acid and LEV, no quantitative reduction in seizure frequency was seen in patient seizure count reports. However, the patient and her family did report an increased awareness of absence seizures following evaluation in the epilepsy monitoring unit. Therefore, it is unclear whether this represents a true increase in absence seizures or just an increase in reporting. No intolerable adverse effects were reported following initiation of valproic acid therapy.

COMMENT

This single case showed a dramatic, rapid effect of LEV discontinuation and reinstitution on generalized spike-wave burst frequency and clinical absence. This effect occurred independently of reduction of LTG and without change in TPM doses, both of which are effective in generalized-onset seizures. Lamotrigine likely also affected this patient’s baseline seizure control because the spike-wave burst frequency decreased to an intermediate level (30-126/h) with restarting LEV and without restarting LTG. The highest spike rate was at 37 to 47 hours after LEV discontinuation, which would correspond to the predicted trough of LEV level. Levetiracetam peak effect is seen at 1 hour, and we began seeing reduction of spike-wave bursts by 3 hours.

Our patient clearly has absence-type seizures, based on clinical and electrographic criteria. However, her age at onset, clinical manifestation, and other seizure types do not correlate well with a known epilepsy syndrome. Based on the history and prolonged video/EEG results, she most likely has an unspecified generalized epilepsy. This analysis of generalized spike-wave frequency as a function of time and maximum LEV dose provides evidence that in this patient LEV dramatically reduced absence seizures in the acute setting. Accurate assessment of long-term absence seizure control was confounded by our inability to accurately count absence seizures as we could with simultaneous video/EEG monitoring. Given the problems with self-reporting of absence-type seizures, quantifying seizure frequency with video/EEG in the epilepsy monitoring unit provides more reliable documentation of clinical response in this patient, albeit during a very short period. Although the ability to generalize from single case studies is limited, this case suggests LEV may be effective in generalized-onset epilepsy and, more specifically, in absence-type seizures. Thus, further study with randomized, controlled trials is indicated.
Accepted for Publication: January 7, 2004.

Correspondence: Michael Privitera, MD, The Neuroscience Institute, Department of Neurology, University of Cincinnati, Medical Sciences Building ML 0525, 231 Albert Sabin Way, Cincinnati, OH 45267 (michael.privitera@uc.edu).

Author Contributions: Study concept and design: Cavitt and Privitera. Acquisition of data: Cavitt and Privitera. Analysis and interpretation of data: Cavitt and Privitera. Drafting of the manuscript: Cavitt and Privitera. Critical revision of the manuscript for important intellectual content: Cavitt and Privitera. Administrative, technical, and material support: Cavitt and Privitera. Study supervision: Cavitt and Privitera.

Funding/Support: This study was supported by an educational grant from UCB Pharma Inc, Smyrna, Ga.

Acknowledgment: The authors would like to thank Nicole Bauer of The Neuroscience Institute, Cincinnati, Ohio, for help in preparation of the figures.

REFERENCES


5. Grant R, Stronven SD. Efficacy and tolerability of 1000-4000 mg per day of levetiracetam: a randomized, double-blind, placebo-controlled study evaluating monotherapy for refractory epilepsy. Epilepsy Res 2000;42:89-95.


