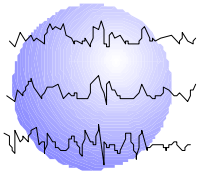
BEHAVIORAL SIDE-EFFECTS OF LEVETIRACETAM

John R. Gates, MD
Catherine Folland, RN
Jennifer Berhow, BA
Gerald L. Moriarty, MD
Patricia E. Penovich, MD



This paper has been prepared specifically for:

American Epilepsy Society Annual Meeting
Seattle, WA
December 6 - 11, 2002
Please consider this information to be preliminary findings.

Minnesota Epilepsy Group, P.A.®
225 Smith Avenue N., Suite 201
St. Paul, MN 55102
Phone: (651) 241-5290
Fax: (651) 241-5248

REVISED ABSTRACT

Rationale: Increasingly, anecdotal reports and small series have described an inordinate incidence of adverse behavioral consequences in patients to whom levetiracetam (LEV *Keppra*®) has been administered. The objective of this study was to evaluate the behavioral side-effect profile of the new antiepileptic drug (AED) *LEV*.

Methods: We retrospectively reviewed patients from the Minnesota Epilepsy Group's database identified as having medically intractable epilepsy to whom LEV was introduced as add-on therapy. Sixty-one patients between 17 and 76 years of age (mean = 41) with histories of medically resistant epilepsy were reviewed for evidence of adverse behavioral consequences. These events were defined as any significant behavioral or mood change requiring medical, psychological or community services/intervention.

Results: Of the 61 patients identified who were on doses of LEV between 500 and 3000 mg/day (mean = 2000), only five patients developed any adverse behavioral consequence. One patient developed depression. Another patient developed a behavior of stealing, inappropriate aggression, and destruction of property. A third patient developed depression and lability in the setting of status post-temporal lobectomy. A fourth patient became irritable, impulsive and experienced increased obsessive and compulsive behaviors. A fifth patient developed aggression and paranoid depression. All of these patients had LEV discontinued with a resolution of symptoms.

Conclusion: In this retrospective study, the evidence of clinically significant adverse behavioral consequences of LEV was only 8%, indicating that the frequency of these events appears to be no higher — and in fact, may be lower — than that reported for the other new AEDs.

Introduction

A previous publication reported an inordinate incidence of adverse behavioral consequences in patients for whom levetiracetam (LEV. *Keppra*®) has been prescribed as adjunctive therapy for epilepsy (Asconape et al.). The objective of this study was to evaluate the behavioral side effects of this new medication in a retrospective review of adult patients with refractory epilepsy to whom LEV had been administered as adjunctive treatment at the Minnesota Epilepsy Group, P.A.®.

Methods:

Patients with refractory epilepsy who received LEV as add-on therapy for at least 6 months were randomly selected from the Minnesota Epilepsy Group database. Sixty-one patients between 17 and 76 years of age (mean = 41) were identified. The histories of these patients were reviewed for evidence of adverse behavioral consequences after the introduction of LEV. Adverse behavioral consequence, for purposes of this study, was defined as any significant behavioral or mood change that did not previously exist and that required a medical, psychological or community service intervention. The review included mood and behavioral assessment for a 12-month period that began 6 months before initiation of LEV and ended 6 months after initiation of LEV. Seizure response was assessed in patients who had quantified seizure data for at least 3 months of follow-up.

Results:

In the group of 61 patients, the total daily dose~~s~~ of LEV ranged from 500 mg to 3000 mg. Five of the 61 patients (8%) developed adverse behavioral consequences during the six months after initiation of LEV. Table 1 identifies these five patients by age and sex; their doses of LEV; their concomitant antiepileptic drugs (AEDs); their LEV level*s* in μg/ml, if available; and their adverse behavioral consequences. As noted in the table, these five patients demonstrated profound changes that required significant intervention. Patient #13 became quite depressed with crying episodes that were not explainable and that resolved with discontinuation of the medication. Patient #41 began stealing and breaking things, which required community police intervention. Patient #43, who was status post temporal lobectomy, became quite depressed and labile in his behavior. This behavior also ceased on discontinuation of LEV. Patient #55 became irritable and impulsive with a dramatic increase in obsessive-compulsive behaviors which also resolved with discontinuation of ~~the~~ LEV. Finally, patient #57 became aggressive, depressed and paranoid, requiring psychiatric hospitalization. This condition also resolved with discontinuation of the medication. Thirty-eight of the 61 patients had quantified seizure data available for at least 3 months of follow-up. Figure 1 shows quantified the seizure response for these 38 patients.

Conclusion:

In this retrospective study, clinically significant adverse behavioral consequences occurred in only 8% of LEV patients, suggesting that the frequency of these events with LEV is no higher — in fact, it is it is possibly lower — than that reported for other new AEDs. However, the adverse reactions that do occur are so dramatic that there could be a disproportionate sense of the frequency of these reactions in the anecdotal recollection of clinicians. A 29% responder rate (52% improvement rate) was identified for the 38 medically refractory patients with > three months follow-up. In a group of 38 refractory patients with ≥ three months follow-up, response rate (≥ 50% seizure reduction) was 29%, and improvement rate (>0% seizure reduction) was 52%.

Reference:

Asconapé JJ, Gerardot JM, Da Costa G. Behavioral changes associated with levetiracetam use in patients with epilepsy. *Epilepsia*. 2001;42(Suppl 7):299.

Table 1

PATIENT #	AGE	LEV DOSE	CONCOMITANT MEDICATIONS	LEV LEVEL	ADVERSE EFFECT
13	26	2000 mg	VPA	18.7	Tired, less happy, crying.
41	33	1500 mg -	LTG, TPM, TGB	18.9	Stealing, breaking things, inappropriate conversation.
43	46	500 mg	VPA	3.8	Depression, lability.
55	39	1500 mg	PHT,. FBM	N/A	Irritable, impulsive, increased OCD
57	22	1500 mg	LTG, GBP	N/A	Aggression, depression, paranoia

Figure 1