CLINICAL EXPERIENCE WITH LEVETIRACETAM (LEV) IN REFRACTORY ADULT EPILEPSY PATIENTS

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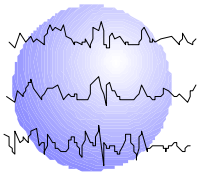

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REVISED ABSTRACT

RATIONALE

Levetiracetam (LEV) is a new antiepileptic drug available for treatment of epilepsy. The efficacy of levetiracetam (LEV) was assessed in a medically intractable adult epilepsy population. Specifically, we determined the percent of responders, the magnitude of their improvement and their optimal dose and blood level range. We also determined the number of patients who showed no response to the drug, and the number who stopped the drug because of side effects. The reader should be able to evaluate the efficacy of LEV and understand a target dose range and blood level range likely to be useful in treatment with LEV.

METHODS

We retrospectively reviewed 44 outpatient charts of adult patients with medically intractable epilepsy who began treatment with LEV between November 2000 and October 2001. Excluded from analysis were patients who had nonepileptic seizure or had surgery for epilepsy while on LEV and those whose seizure counts were not reliable. Seizure type and frequency were tabulated using reports of the patient, family, or caregiver as documented in the medical record. Seizure counts were determined for the 6 months prior to LEV use and compared with a minimum of 6 months after initiation. Demographics, seizure types and frequency, number of previous AEDs, number of concomitant AEDs, adverse events, dose at time of best response, and corresponding blood levels were recorded when available. Patients were identified who stopped LEV because of side effects, and the nature of their side effects was recorded.

RESULTS

Forty-four patients met inclusion criteria including 25 males and 19 females (ages 18-67, mean 40 years). Five (11%) discontinued LEV because of side effects: 3 because of behavior change; 1 due to gait disturbance; 1 due to depression. Eleven (25%) had no significant improvement and discontinued LEV. Nine (20%) had no improvement but remained on LEV. Nineteen (43%) responded to treatment: 8 became seizure free; 6 had 75% –> 100% reduction in seizures; 3 had 50% -> 75% reduction; 2 had 25% -> 50% reduction. Mean dose at the time of maximum efficacy in the 19 responders was 1,7980.5 mg/day (range 1000-3000 mg/day). Mean LEV blood levels at the time of maximum efficacy were available for 14 responders 22 μg/mL and for 11 nonresponders 26.7 μg/mL.

CONCLUSION

Forty-three percent of the 44 medically intractable adults responded to LEV with ≥ 25% reduction in seizure frequency, with 8 becoming seizure free. Eleven percent stopped LEV due to side effects. LEV appears to be a very useful drug in this intractable population.

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RATIONALE

Levetiracetam (*LEV. Keppra®) is a new antiepileptic drug (AED) for treatment of epilepsy. There have been few previous studies addressing efficacy and tolerability in relation to dose and blood levels. The objective of the present investigation was to identify the dose and blood level associated with maximum seizure reduction.

METHODS

We retrospectively reviewed the charts of 44 adult outpatients with medically intractable epilepsy who began treatment with LEV between November 2000 and October 2001. Patients were not included if they had a history of nonepileptic seizures, surgery for epilepsy while on LEV, or unreliable seizure counts. Five of the 44 patients were excluded following discontinuation of LEV secondary to adverse events. These consisted of behavior changes (3 patients), depression (1 patient), or gait disturbance (1 patient). For the remaining patients, seizure counts were determined for the six months prior to LEV use and compared to seizure counts a minimum of six months after initiation. Subjects were divided into two groups based on change in seizure frequency. Subjects with < 25% improvement in seizure frequency were classified as non-responders. All subjects who had a ≥ 25% decrease in numbers of seizures were classified in the responder group. Among the responders, subjects were classified as seizure-free, ≥ 75% improvement in seizure frequency but not seizure free, 50% to < 75% improvement in seizure frequency, or 25 to < 50% improvement in seizure frequency.

LEV dose and blood levels (when available) were recorded at the optimum level of seizure control for each patient in the responder group. For non-responders, the highest dose administered and blood levels (when available), were used for comparison purposes. Seizure type(s) recorded for each patient were classified as partial, partial-onset, partial-onset with secondary generalization, or multifocal with secondary generalization. Number of previous and concomitant AEDs were also recorded. Variables were compared for the responder and non-responder groups using t-tests for independent samples.

RESULTS

Nineteen patients (10 males and 9 females; mean age = 41.5 years) responded to treatment, while 20 patients (10 males and 10 females; mean age = 37.8 years) were classified as nonresponders (Figure 1).

Mean dose at time of maximum efficacy in the 19 responders was 1789.5 mg/day (range = 1,000 mg - 3000 mg, s.d. = 630.6 mg/day). For the non-responders, the mean maximum dose was 2506.3 mg/day) (range = 500 mg/day – 4,000 mg/day; s.d. = 652.0 mg/day). This difference was significant: p = 001 level (Fig. 3a). LEV blood levels at time of maximum efficacy were available for 14 patients in the responder group (mean = 22.4 μg/mL; range – 13-42 μg/mL; s.d. = 7.8 μg/mL) and for 11 patients in the

nonresponder group (mean = 26.7 μg/mL; range = 3.8 – 40.2, s.d. = 10.2). This difference was not statistically significant (Figure 3b).

Among patients who responded to treatment, LEV dose and blood levels were also examined comparing patients with excellent outcome (seizure free or ≥ 75% seizure reduction) to those with a reduction in seizures ranging from 25 to < 75% (Figure 4). There was no significant difference in LEV dose between the two groups (≥ 75% = 1714.3 mg/day; 25 – < 75% = 2000 mg/day) (Figure 4a). However, patients who experienced excellent seizure outcome were found to have significantly lower LEV blood levels at the time of maximum efficacy compared to patients with more modest improvement in seizure frequency (≥ 75% = 20.2 μg/mL; p = < .05) (Figure 4b).

There was no difference between responders and non-responders in the incidence of any seizure type. Number of previous and concomitant AEDs also did not differ between the two groups (previous AEDs: responders = 6.05 versus non-responders = 6.65; concomitant AEDs: responders = 1.53, non-responders = 2.05).

Five patients discontinued LEV because of adverse events. Three of the 5 patients experienced exacerbation of preexisting psychiatric disorders, including increased aggressive oppositional behavior and paranoia (n =- 1). Increased depression (n = 1), and increased symptoms of Tourette's syndrome and obsessive-compulsive disorder (n = 1). I*n addition, 1 patient discontinued due to depression (new-onset) and another because of gait disturbance. These 5 patients discontinued LEV after an average of 70 days on therapy. Six additional patients who had previous histories of psychiatric disorders (aggression, agitation, impulsivity, and psychosis) did not experience any exacerbation of these problems.

CONCLUSIONS

- For adult patients with intractable epilepsy, maximum efficacy may be associated with lower LEV doses than previously reported. This paradoxical finding is consistent with at least 1 previous study in which seizure-free status was attained for some patients at doses as low as 500 mg/day (Smith and Humason, 2001)
- Patients who respond to LEV therapy appear to achieve maximum benefit at mean daily doses significantly below those of nonresponders.
- Lower blood levels of LEV may be associated with maximum seizure control.
- Concerns regarding a higher incidence of behavioral side effects with LEV are not supported in our sample. The incidence of behavioral side effects may be lower than previously suggested (Asconapé et al, 2001).

REFERENCES

1. Asconapé JJ, Gerardot JM, Da Costa G. Behavioral Changes associated with levetiracetam use in patients with epilepsy. *Epilepsia* 42(S7): 299, 2001.
2. Smith BJ, Humason KA. Efficacy of levetiracetam as adjunctive therapy in partial epilepsy. *Epilepsia* 2001;42(suppl 7:187.

Figure 1

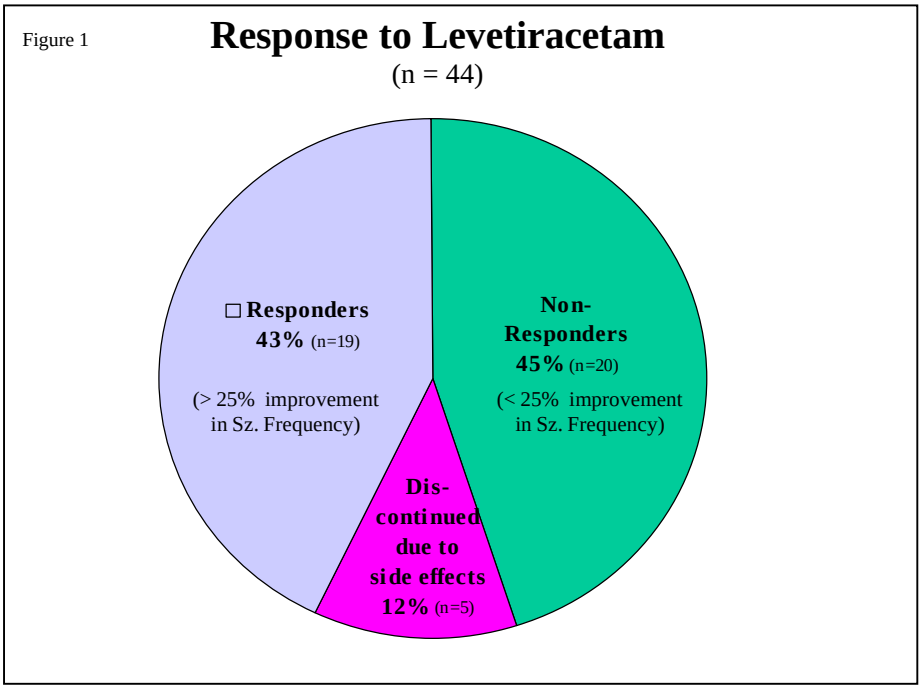


Figure 2

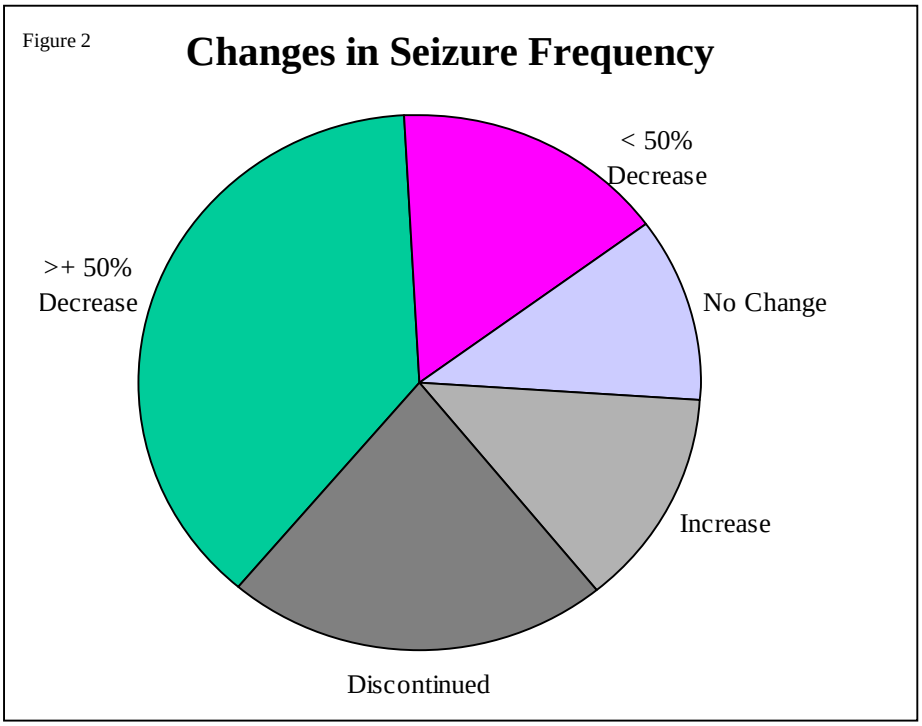


Figure 2

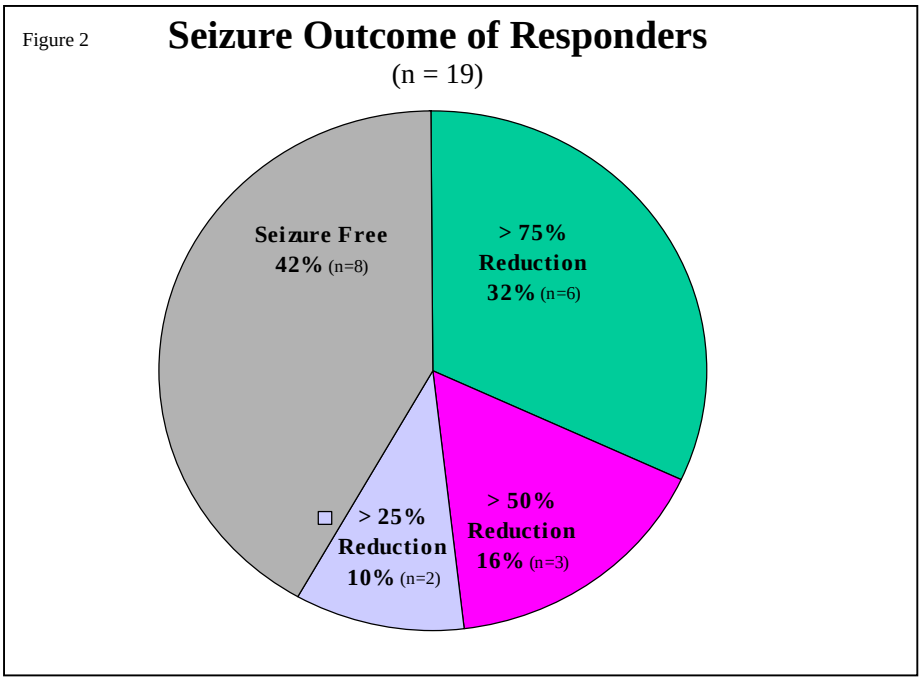
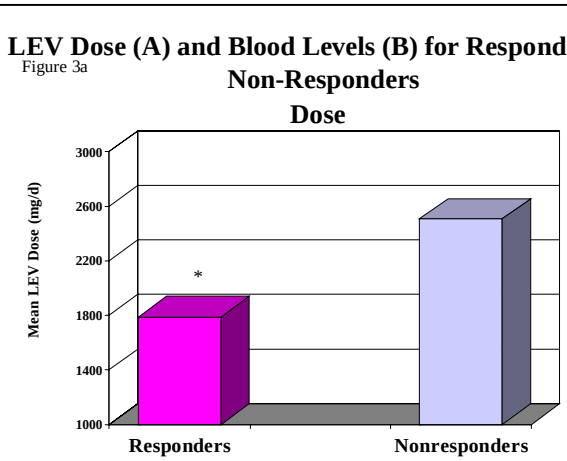


Figure 3a



*p < .001

Figure 3b

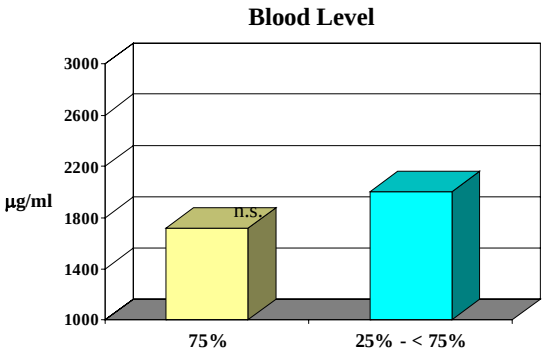


Figure 4a

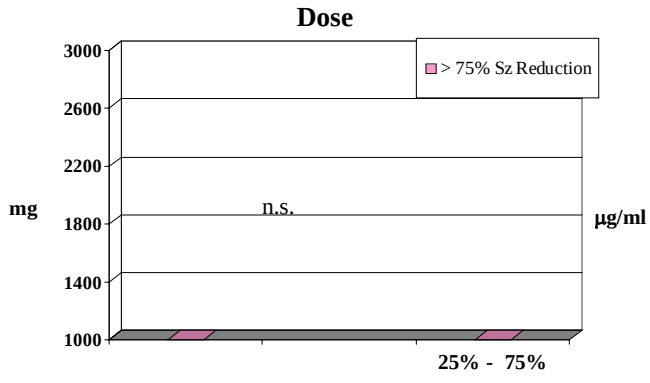
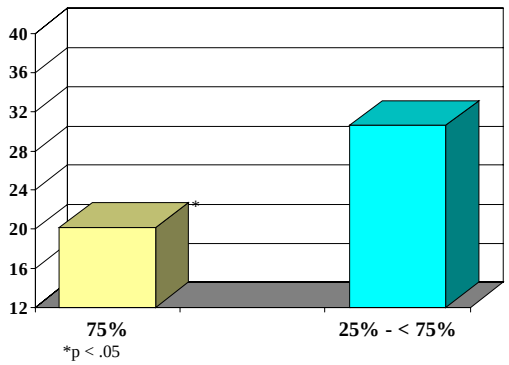


Figure 4b



*p < .05