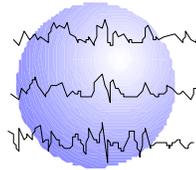


BEHAVIORAL AND EMOTIONAL EFFECTS OF LEVETIRACETAM IN CHILDREN WITH INTRACTABLE EPILEPSY

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ABSTRACT

RATIONALE: The objective of this study is to review and analyze the impact of levetiracetam (LEV) on the emotions and behaviors of children with intractable epilepsy.

METHODS: Medical records of 115 consecutive children ages 1- to 11-years who had been treated with LEV for intractable epilepsy were reviewed for: 1) demographics, 2) history of behavior problems, 3) history of previous medications causing behavioral or emotional problems, and 4) changes in behavior or emotional status following treatment with LEV.

RESULTS: There were 63 children with a history of behavioral or emotional problems. After initiating treatment with LEV, parents reported that 18 (29%) had worsening of behavioral problems, 25 (40%) had no change and 20 (31%) reported improvements in behavior. Sixty-five percent of this group had a history of behavioral problems caused by previous treatments. Of the 52 children with no history of behavioral or emotional problems, 42 (80.8%) were unchanged, 5 (9.6%) were reported as doing better, and 5 (9.6%) developed behavioral or emotional problems. Thirty percent of those developing problems in this group had a history of behavioral problems caused by previous treatments. The most common problems reported by both groups were: aggressiveness 20 (87%) and oppositional behaviors 16 (70%). Emotional problems were worse in all children with exacerbations of behavior, and were isolated in 3 (2.6%) of the children.

CONCLUSIONS: A history of behavioral and emotional problems appears to predispose children to an exacerbation of these problems when treated with LEV. However, many parents of children in this group (31%) also reported improvements. The children whose behavior worsened were also more likely to have a history of previous treatments causing similar problems (65%). Ten percent of the group of children with no history of behavioral or emotional problems developed these side-effects from treatment with LEV.

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RATIONALE

Pediatric patients seen at the Minnesota Epilepsy Group, P.A.[®], have been treated with levetiracetam (LEV, Keppra[®]) for both partial and primarily generalized seizures. Clinical experience with LEV in the pediatric population supports LEV as a safe and effective medication. A previous comprehensive review of 115 children revealed the most common adverse side effect experienced was the exacerbation or development of behavioral and/or emotional problems¹. Other retrospective series involving LEV in pediatric patients show similar findings^{2,3}. Published studies report limited information on the characteristics of the behavioral/emotional side effects. The objective of this study was to review and analyze the impact of LEV on the emotions and behaviors of children with intractable epilepsy.

METHODS

Medical records of 115 consecutive cases of children (1 to 11 years of age) who had been treated with LEV for intractable epilepsy were reviewed for: 1) demographics, 2) history of underlying behavioral/emotional problems, 3) history of previous medications causing or exacerbating behavioral or emotional problems, and 4) changes in behavior or emotional status following treatment with LEV. An underlying behavioral or emotional condition is one that has etiology innate to the child and is not precipitated by treatment or environmental factors. At each clinic visit, parents/caregivers were questioned about the patient's mood and behavior. Reports from parents/caregivers and from school personnel were documented. Non-parametric analyses were used to evaluate significance.

RESULTS

Demographics for the 115 patients are summarized in Table 1.

Table 1. Patient Demographic and Baseline Characteristics

Variable	Value (n=115)
Males/Females (n)	61/54
Age (y), Median	5.5
Number of Prior AEDs Failed, Median	7.0
Cognitively Impaired (%)	87%
Underlying Behavioral or Emotional Problem (n, %)	63 (55%)
No underlying Behavioral or Emotional Problem (n, %)	52 (45%)

Sixty-three children (55%) had an underlying behavioral or emotional problem (Group 1), while 52 children (45%) had no underlying behavioral or emotional problems (Group 2). Sixty-five percent of Group 1 had a history of worsening behavioral/emotional problems caused by 1 or more previously prescribed antiepileptic drugs (AEDs). In Group 2, 20% of patients had developed a behavioral/emotional problem with one or more previously prescribed AEDs.

After children in Group 1 had initiated treatment with LEV, their caregivers had reported that the behavioral problems of 18 of the children (29%) had worsened, 25 children (40%) were unchanged, and 20 children (32%) had improvements in behavior. Caregivers of children in Group 2 reported that after those children initiated treatment with LEV, 42 (81%) were unchanged, 5 (10%) were doing better, and 5 (10%) had developed behavioral or emotional problems (Figure 1).

The percentage of patients with improvement in behavior and/or mood was significantly greater for children with an underlying behavioral or emotional problem (Group 1) compared with children with no underlying behavioral or emotional problem (Group 2); $p = .004$. The percentage of children with worsening of behavioral or emotional problems was also significantly greater for Group 1 than for Group 2; $p = .001$.

Nineteen patients discontinued LEV due to adverse behavior/mood and 18 of those 19 patients had also previously discontinued one other AED for worsening behavioral or emotional problems. All 18 of these latter patients were included in Group 1 (Figure 1).

A total of 23 children had a worsening of behavior and/or mood with LEV treatment: 18 children in Group 1 and 5 children in Group 2. The adverse behavioral/emotional changes observed with LEV treatment for these 23 children are described in Table 2. Emotional problems were worse in all children who had exacerbations of behavior and were isolated in 3 (3%) of the children.

DESCRIPTION OF ADVERSE BEHAVIOR/EMOTIONAL CHANGES WITH LEVETIRACETAM	
Table 2	n=23
Description of Change	Number of Patients (%)
Aggressiveness:	20/23 (87%)
Oppositional Behavior:	16/23 (70%)
Emotional Lability:	23/23 (100%)

The 115 children received a median initial LEV dose of 8.6 mg/kg/day and a median maximum LEV dose of 46.0 mg/kg/day. Children with adverse behavioral effect(s) with LEV treatment received a lower median initial and maximum LEV dose than children

with no behavioral adverse effect(s) with LEV: 8.3 mg/kg/day and 40.4 mg/kg/day versus 8.7 mg/kg/day and 47.1 mg/kg/day, respectfully. Most patients (70%) increased their dose intervals at least every two weeks, and the remaining patients increased their dose weekly (20%) or after less than 7 days (10%) (Table 3).

Table 3. Dosing/Titration		
	Median Initial Dose (mg/kg/day)	Median Maximum Dose (mg/kg/day)
Dosing Characteristics		
All	8.6	46.0
Behavioral adverse effect	8.3	40.4
No behavioral adverse effect	8.7	47.1
Titration Characteristics		
Increased dose at intervals every 2 weeks	70%	
Increase dose weekly	20%	
Increased dose at intervals < 7 days	10%	

CONCLUSIONS

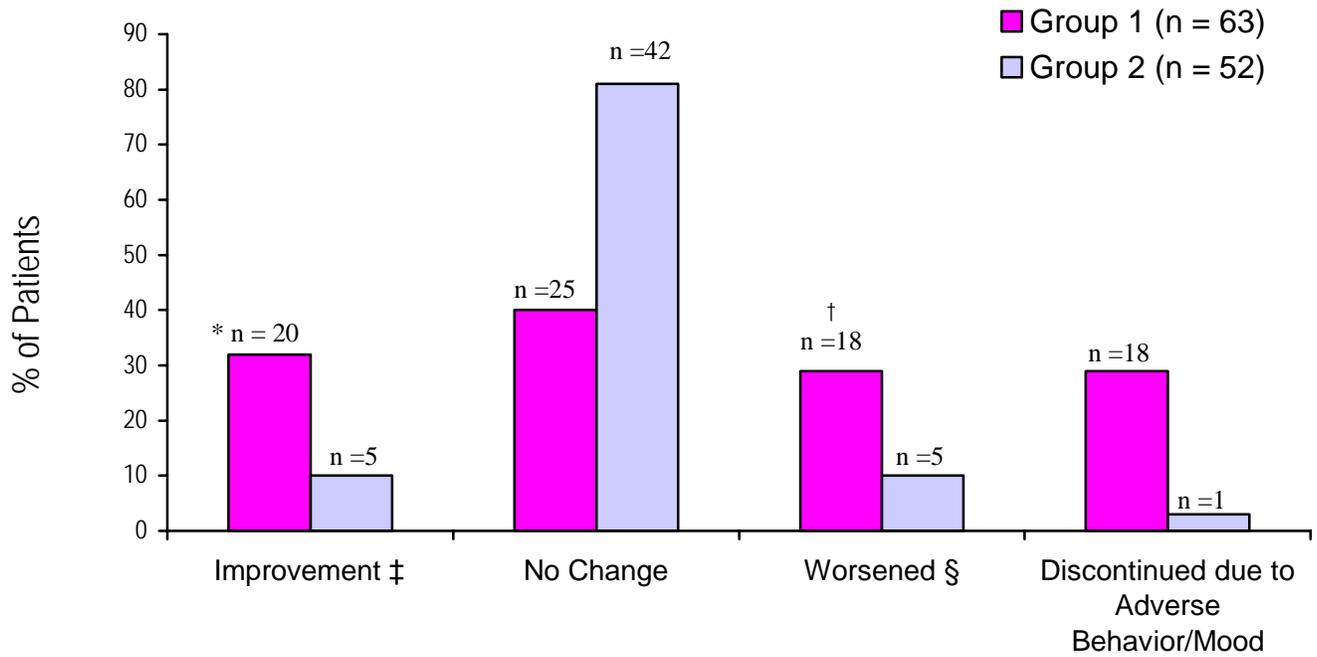
- An underlying behavioral or emotional problem appeared to predispose children to a change in behavioral status with LEV treatment; however, an underlying problem did not predict whether LEV treatment would improve or exacerbate the behavior, since the percentage of patients reporting each outcome was similar.
- Sixty-five percent of children whose underlying behavioral/emotional problem worsened with LEV had a history of previous treatments causing similar problems.
- Of the children without underlying behavioral or emotional problems, nearly one-third developed these side effects with at least one previous AEM, but only one-tenth developed them with LEV.
- Changes in behavioral or emotional status did not correlate with initial dose, maximum dose or dosing titration, although all children were treated similarly.

REFERENCES

1. Gustafson MC, Ritter FJ, Frost MD, et al. Clinical Experience with Levetiracetam Treating Refractory, Symptomatic Seizures in Children: Poster presented at: Annual Meeting of the American Epilepsy Society: December 3, 2001; Philadelphia, PA
2. Bourgeois, B. et al. "Open-Label Assessment Of Levetiracetam Efficacy And Adverse Effects In A Pediatric Population". *Epilepsia* 42 (suppl 7) 2001; 53.
3. Yu-tze Ng and James W. Wheless. "Levetiracetam: Pediatric Experience". *Epilepsia* Vol 42 (suppl 7) 2001, 55.

Figure 1

Change in Behavior or Mood After LEV Treatment



* p = .004

† p = .011

‡ Reports of improvement involved only changes in mood with children described as being "happier"

§ Behavior and/or Mood