

The Effects of Levetiracetam on Neuropsychological Functioning in Relation to "Subclinical" Spike Production

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Rationale

The objective is to determine if levetiracetam (LEV, Keppra®) can improve neuropsychological functioning in children manifesting evidence of "subclinical" spike production.

Background

There has been concern that interictal spikes, particularly rolandic spikes, with or without clinical seizures, can be associated with attention deficit hyperactivity disorder and deficits in visual perception, short-term memory, and overall cognitive functioning (Deonna et al, 2000; Holtmann et al, 2003; Weglage et al, 1997). In children with benign epilepsy with centrotemporal spikes (BECTS), LEV has been shown to reduce seizure frequency and cause normalization of electroencephalography (EEG) (Bello-Espinosa and Roberts, 2003). LEV is a novel antiepileptic drug that is indicated for use as adjunctive treatment of partial onset seizures in adults and children 4 years of age and older with epilepsy. Thus, we hypothesized that children with attentional/learning difficulties and "subclinical" spikes would have improvement of neuropsychological functioning if treated with LEV.

Methods

Subjects with learning difficulties, EEG findings of focal spike discharges, and Leiter International Performance Scale-Revised (Leiter-R) scores >70 were enrolled. Neuropsychological testing (Wide Range Assessment of Memory and Learning, Second Edition [WRAML2; Sheslow and Adams, 2003] and Wechsler Individual Achievement Test®, Second Edition [WIAT-II]-Abbreviated [Psychological Corporation, 2001]) was completed at baseline and after 10 weeks of LEV therapy. Digital, 128-channel dense-array EEG recordings (Electrical Geodesics, Inc) were done throughout each testing session. Additional endpoints incorporated scores from Clinical Global Impression (CGI) scales, including CGI-Severity of Illness at baseline and CGI-Improvement and CGI-Efficacy at the end of the study (Figure 1). LEV was started at 10 mg/kg/day and then titrated weekly by 10 mg/kg/day up to a tolerable dose, with the goal of a maximum of 40 mg/kg/day. Dosing was divided to twice daily. After study completion, subjects were offered LEV by prescription.

Figure 1. Clinical Global Impression Scale Scoring*

CGI-Severity of Illness [†]		CGI-Improvement [‡]	
0 = Not assessed		0 = Not assessed	
1 = Normal, no impairment		1 = Very much improved	
2 = Borderline impairment		2 = Much improved	
3 = Mild impairment		3 = Minimally improved	
4 = Moderate impairment		4 = No change	
5 = Marked impairment		5 = Minimally worse	
6 = Severe impairment		6 = Much worse	
7 = Extreme impairment		7 = Very much worse	

CGI-Efficacy [‡]				
Therapeutic Effect	Side Effects			
	None	No Interference	Interferes With Function	Outweighs Therapeutic Effect
Marked: Significant Improvement	1	2	3	4
Moderate: Partial Remission	5	6	7	8
Minimal: Slight Improvement	9	10	11	12
Unchanged or Worse	13	14	15	16

* Adapted from Guy, 1976.
[†] In reference to attention/learning abilities.
[‡] Compared with baseline.

Pretreatment and posttreatment test scores were compared by calculating the difference (ie, posttreatment minus pretreatment) and comparing it with both the standard error of measurement (SEM) for each index and the standard retest gain for each subtest (based on the published standardization data for each test). The hypothesis that test scores would be higher in the posttreatment administration was assessed as follows: difference scores that were larger than the combined SEM and retest gain for that index or subtest were considered to indicate significant improvement on that index or subtest.

Subject Summaries

Subject A

The subject was an 8-year-old male with the first seizure event 1 year before the study. Ictal manifestations involve speech arrest and garbled speech. Events were mostly nocturnal and awakened the subject, although some daytime episodes have occurred. The baseline EEG revealed sharp- and slow-wave discharges maximal over the right parietal region, which on further digital electrical source localization were topographically mapped to the right central region; no clinical phenomena were noted during the baseline EEG. Magnetic resonance imaging (MRI) was normal. Other significant medical history included asthma, tonsillectomy and adenoidectomy at age 2 because of recurrent otitis media infections, difficulty settling to sleep, and nocturnal enuresis. There was no family history of epilepsy.

Neurodevelopmental history was noteworthy for early articulation difficulties resolved by age 5 years, early intervention and preschool disabilities services (but the subject attended mainstream kindergarten), and, currently while in third grade, difficulty following directions, poor focus and attention, and slowness in completing work. His neurological examination was within normal limits.

Subject A became irritable and had difficulty falling asleep on LEV 30 mg/kg/day, so he was maintained on 20 mg/kg/day. He experienced only 1 clinical event during the study, consisting of garbled speech for 10 seconds; this event occurred after a missed dose of medication.

Subject B

The subject was a 10-year-old female with a history of inattentiveness and episodes of staring. Baseline EEG revealed frequent spike- and slow-wave discharges that had electrical source localization to the right central region; there were no clinical phenomena noted during EEG. MRI was unremarkable except for a 5-mm pineal cyst. Her medical history was significant for a previous diagnosis of central auditory processing disorder, poor social skills, anxiety, obsessive-compulsive behaviors, sensory issues, dyspraxia, constipation, and myopia corrected with glasses. She achieved her neurodevelopmental milestones at age-appropriate times. She is maintained in a mainstream classroom with supplemental educational support. Her educational profile is noteworthy for poor reading comprehension, difficulty with mathematics, and poor writing skills. A trial of atomoxetine in 2004 was discontinued because of lack of efficacy. Her neurological examination had brisk deep tendon reflexes but was otherwise within normal limits.

Subject B was titrated to LEV 40 mg/kg/day. No clinical seizure phenomena were reported during the study. Her teacher reported improvement in organizational skills and short-term memory.

Subject C

The subject was a 10-year-old female with a history of inattentiveness. Her medical history was significant for word-finding and memory difficulties and a previous diagnosis of central auditory processing disorder. Early neurodevelopment was age appropriate. However, it was noted in preschool that she had difficulty with prereading and math skills. Currently, she is in a special education classroom setting. She is described as having difficulties with verbal tasks and short-term memory. She is also described as being disorganized and forgetful. Family history is significant for a maternal second cousin with epilepsy. Baseline EEG was significant for recurrent spike- and slow-wave discharges, which on digital source localization were topographically mapped to the left occipital region and/or left medial parietal lobe; there were no associated clinical phenomena observed during the baseline EEG. MRI was unremarkable. Neurological examination was within normal limits.

Subject C was titrated to 40 mg/kg/day of LEV. No clinical episodes of seizure were noted during the study. The family reported that the subject was "more responsible."

Results

Three subjects were enrolled, 2 females and 1 male (mean age, 9.5 years). Results of psychometric testing were as follows:

WRAML2: Analysis of pretreatment and posttreatment scores for the 3 participants indicated a significant improvement on all indexes for 2 subjects and on 2 indexes for the third subject (Table 1).

Table 1. WRAML2 Results*

	Pretreatment	Posttreatment	Difference
Verbal Memory Index	72/62/67	94/82/82	+22 [†] /+20 [†] /+15 [†]
Visual Memory Index	82/63/91	118/85/100	+36 [†] /+22 [†] /+9
Attention/Concentration Index	88/79/65	103/97/65	+15 [†] /+18 [†] /0
General Memory Index	74/60/66	106/84/76	+32 [†] /+24 [†] /+10
Screening Memory Index	72/57/74	107/80/89	+35 [†] /+23 [†] /+15 [†]

	SEM	Gain	Total
Verbal Memory Index	4.5/4.5/4.5	6.3/6.3/6.3	10.8/10.8/10.8
Visual Memory Index	5.8/5.4/5.4	7.2/7.2/7.2	13.0/12.6/12.6
Attention/Concentration Index	6.2/5.2/5.2	1.7/1.7/1.7	7.9/6.9/6.9
General Memory Index	4.7/4.0/4.0	6.7/6.7/6.7	11.4/10.7/10.7
Screening Memory Index	4.7/4.2/4.2	8.1/8.1/8.1	12.8/12.3/12.3

SEM = Standard error of measurement; SEM and retest gains are from standardization data (Sheslow and Adams, 2003).

* Scores are listed for subjects A/B/C, respectively.

[†] Statistically significant.

WIAT-II-Abbreviated: None of the WIAT-II subtest pretreatment/posttreatment difference scores were larger than the combined SEM and gain for that subtest for subjects A or B, but there were 2 significant subtest improvements for subject C, who showed significant gains (ie, larger than SEM plus gain) on both Word Reading and Spelling.

CGI Scales: Results of clinician-rated CGI scales revealed that subjects A and B had significant improvement over the course of the study and subject C had minimal improvement (Table 2).

Table 2. Clinical Global Impression Scale Results

Subject	CGI-S*	CGI-I [†]	CGI-E [‡]
A	3	2	8
B	4	2	5
C	4	3	9

* CGI-Severity; done at baseline.

[†] CGI-Improvement; done at the end of the study.

[‡] CGI-Efficacy; done at the end of the study.

Discussion

Overall, the results strongly support the hypothesis that posttreatment scores are significantly higher than would be predicted based on the combined effects of error and practice effects for the WRAML2, which assesses memory and attention, but not for the WIAT-II-Abbreviated, which assesses academic achievement. Thus, this cohort of 2 children with spike activity who did not have identifiable clinical seizure manifestations (subjects B and C) and 1 child with interictal spike activity and a history of ictal phenomenology suggestive of BECTS (subject A) had demonstrable deficits in memory and attentional function at baseline that significantly improved after 10 weeks of LEV therapy.

Academic achievement scores did not change significantly from baseline, but academic achievement will lag by months after improvement in memory and attention. Follow-up testing is being planned to determine if initial improvements in attention and memory may predict later improvements in academic achievement.

This study adds to the literature that suggests "subclinical" interictal spikes might not be benign but rather might be responsible for memory and attentional deficits, and thus could adversely affect a child's ability to learn. Furthermore, this study suggests that the antiepileptic drug LEV can ameliorate these memory and attention deficits.

Additionally, this study suggests that "subclinical" spike activity should be considered in certain subsets of children with learning and/or attention difficulties.

Further research is necessary to determine if the treatment findings are sustainable over longer periods of time. Further analysis of EEG findings is planned to determine if the neuropsychometric results and response to LEV correlate with spike quantity or localization.

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