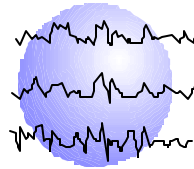


USE OF LEVETIRACETAM (LEV) IN CHILDREN UNDER 2 YEARS OF AGE

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Please consider this information to be preliminary findings.

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REVISED ABSTRACT

Rationale: Levetiracetam (LEV, Keppra[®]) was approved for use in patients, 16-years of age and older, as an adjunctive treatment for partial onset seizures, and launched in the USA in April 2000. Since then there has been little information regarding its use in children, particularly young children. The objective of this study was to better understand the use of LEV in children <2 years of age.

Methods: We reviewed our use of LEV in children <2 years of age at Minnesota Epilepsy Group[®]. Patients who were <2 years of age at the time they were started on LEV were identified. Their records were reviewed for starting dose (mg/kg), maximum dose (mg/kg), titration rate, tolerability and efficacy. Seizure type and epilepsy syndrome were also documented. LEV levels, blood counts and serum characteristics were not routinely drawn in all patients.

Results: Twenty-two children < 2 years of age were identified. Ages ranged from 2 days to 21 months. There were four new onset seizure disorders, the remainder having different epileptic syndromes (including infantile spasms). Initial dosages ranged from 10 mg/kg/day to 41 mg/kg/day (median 18.4-mg/kg). Maximum dosages ranged from 15-mg/kg/day to 144-mg/kg/day (median 61.25-mg/kg) and were achieved after several days to six weeks. Four patients received LEV as their first anticonvulsant. Six patients received LEV as their second anticonvulsant. Six patients received LEV as monotherapy. Twelve out of 20 patients continued LEV. Two patients were lost to follow-up. Six patients were reported to have side-effects that included a slight increase in hyperactivity, becoming a "zombie," or fatigue (as described by caregivers). Side-effects did not appear related to titration rate or maximum dose. Of the 8 patients known to discontinue LEV, 1 discontinued due to side-effects and 7 patients discontinued due to a lack of benefit. Of 20 patients, 4 patients were seizure-free, 6 had a >90% reduction in seizures and 12 patients had a >50% reduction in their seizures. Eight patients did not have a significant change.

Conclusion: LEV appears to be a safe, well-tolerated and effective anticonvulsant in young children. A faster titration rate and higher maximum dose were used in these children without an increase in significant side-effects. Therefore, LEV may be considered as a first-line anticonvulsant in neonates and children <2-years of age.

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INTRODUCTION:

Clinical experience and trials involving the newer anti-epileptic drugs (AEDs) in neonates and infants are limited. To date, no published data details the use of LEV in this population. The objective of this study was to examine the use of LEV in children less than two years of age.

METHODS:

Hospital and clinic records of children seen at the Minnesota Epilepsy Group, P.A.® were reviewed to identify all children who began LEV treatment prior to two years of age. Records were reviewed for dosing, titration, tolerability and efficacy. Seizure type/epilepsy syndrome were also documented. LEV levels and complete blood counts (CBCs) were not routinely obtained on all patients, but were included for analysis when available. LEV concentrations were measured by MedTox Laboratories, St. Paul, MN, USA, using liquid-liquid extraction followed by gas chromatography with flamed-ionization detection.

RESULTS:

Two neonates and 20 infants initiated LEV. Two patients were lost to follow-up before adequate information could be obtained regarding the treatment trial. Demographic information and baseline characteristics for all 22 children are reported in Table 1.

Variable	Value
Males/Females	8/14
Age at Initiation of LEV, Median (range)	15 months (2 d– 22 mo)
Weight at Initiation of LEV, Median (range)	9.7 kg (3.4 – 12.1 kg)
Median Number of Previously Failed AEDs, Median (range)	2(0-8)
Number of Patients With Partial Onset Seizures	19
Number of Patients With Infantile Spasms	3

All of the patients had either partial onset or multifocal (mixed) seizure types. Etiologies included a degenerative neurologic process (not specifically identified), CNS malformations (including cortical dysplasia and Dandy Walker syndrome), and hypoxic and/or ischemic injuries (i.e., infarcts).

Administration

Patients received LEV orally as halved or quartered tablets as a solid dose, or crushed and mixed in a spoonful of food such as applesauce or pudding. For some patients, the dose was dissolved in a small amount (5 – 15 mL) of water. Ten patients received the initial starting dose b.i.d., and the remaining 10 patients received the initial starting dose once a day. The median initial dose being 18.1 mg/kg/day (range 10.4 – 27.7 mg/kg/day) with twice-daily dosing in 19 of the 20 patients.

Titration rate

Rates varied between patients. Increases in dose were made every one to six days in 9 patients, weekly in 5 patients, and every 8 or more days in 4 patients. In 1 patient, no increase in dose was made because seizure freedom was achieved. In one patient, there was poor documentation of the titration rate. The median dose was 61.25 mg/kg/day (range 15 – 144 mg/kg/day), with twice-daily dosing in 19 of 20 patients.

Concentrations

Four of twenty patients had LEV concentrations drawn and morning trough levels were identified in all 4 of those patients. Those 4 patients received LEV twice daily, morning and at bedtime. All levels were measurable, but varied with respect to dose. A total of 6 trough levels were identified, including 3 levels from 1 of the 4 patients: one level at 48 mg/kg/day and two levels at 96.1 mg/kg/day (Figure 1). Trough concentrations ranged from 2.4 mg/L on 44.6 mg/kg/day to 33.6 mg/L on 53.5 mg/kg/day.

Responder rates

Although not an efficacy study, we did look at responder rates (Figure 2). One out of 3 patients with infantile spasms responded to LEV with an 85% decrease in number of clusters of spasms. It should be noted that these three patients had previously been treated with and failed 2 to 6 AEDs. Four patients, including both neonates, received LEV as their first maintenance AED. All 4 patients were responders, with both neonates remaining seizure free on monotherapy. Two other children, each failing 1 previous AED, became seizure free on LEV monotherapy. Median initial and maximum doses were similar for the responders and the non-responders (Table 2). Twelve patients continue LEV with a median treatment duration of ten months (mean = 12.5 months; range = 4-265 months). The remaining 8 patients discontinued LEV due to adverse events (1 patient), or a lack of benefit (7 patients).

	n	Median Initial Dose mg/kg/day	Median Maximum Dose mg/kg/day
All	20	18.1 (10.4 – 27.7)	61.25 (15-44)
Responders	12	12.8 (10.4 – 27.7)	50.0 (15.8 – 111)
Seizure Free	4	16.6 (12.4 – 20.3)	18.9 (15.8 – 56.8)
Non-responders	8	20.7 (12-8-23.5)	70.7 (51.2 – 144.3)
Adverse Effects	6	18.2 (10.4 – 27.7)	69.6 (15.8 – 111)
No Adverse Effects	14	14.8 (10.4 – 23.5)	59.6 (18.9 – 144.3)

Side Effects

Side effects were reported in 6 of the 20 patients and were considered mild and/or transient in all but one patient who discontinued LEV due to sedation. The one patient who had an unidentified neurodegenerative disease died as the result of a cardiopulmonary arrest felt to be unrelated to LEV. Titration rate did not appear to correlate with side effects in this small group of patients. Median initial and maximum doses were similar in the patients who experienced side effects and those who did not (Table 2). CBCs were obtained on 8 patients during LEV therapy. No abnormal laboratory values were reported.

CONCLUSIONS:

- In children less than 2 years of age, LEV can be easily administered orally, either as a solid or crushed and mixed with food or water
- LEV appears to be absorbed with measurable trough concentrations on twice daily maintenance dosing, though daily dose does not appear to correlate with serum LEV levels
- LEV efficacy in partial onset seizures in children less than 2 years of age appears independent of starting or maximum dose and coincides with efficacy in adults (Folland and Moriarty, 2002)
- Adverse effects appear minimal and unrelated to starting or maximum LEV doses

Figure 1. Levetiracetam Trough Concentrations*

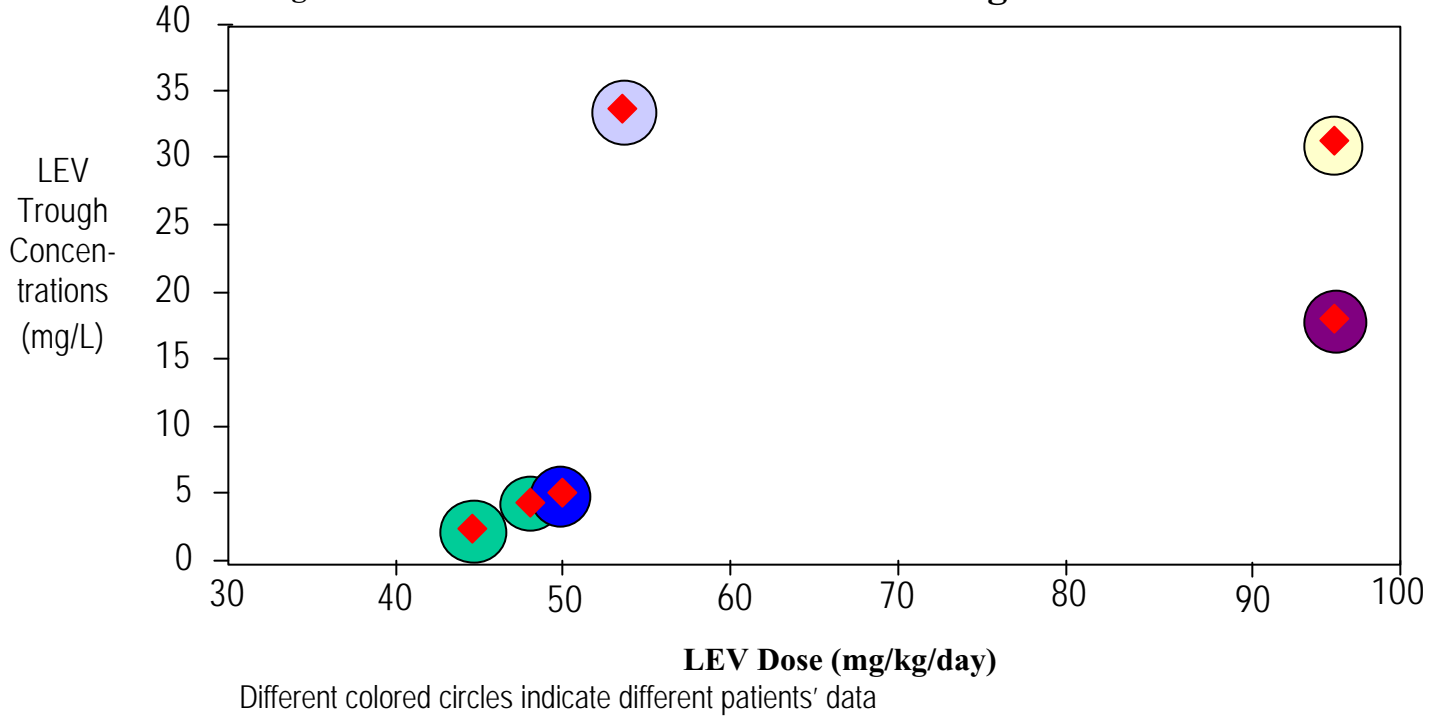
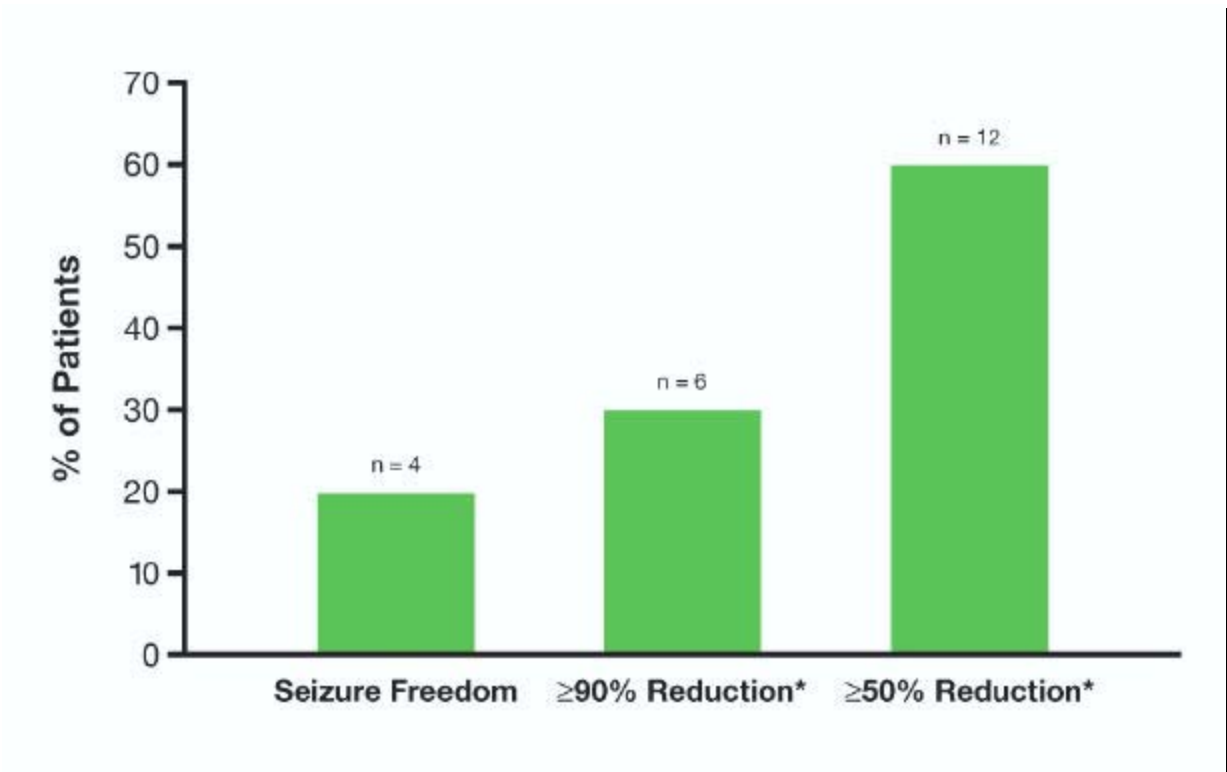


Figure 2

Seizure Reduction



* Numbers are cumulative. Twenty of the 22 patients reviewed were included in the efficacy evaluation since the other 2 patients were lost to follow-up before adequate information was obtained regarding treatment.