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BRIEF COMMUNICATION

High-dose intravenous levetiracetam for acute seizure exacerbation in children with intractable epilepsy

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Summary

We review our experience with high-dose intravenous levetiracetam (IV-LEV) for acute seizure exacerbations in nine children with medically intractable epilepsy. All children had acute repetitive seizures—while on chronic antiepileptic drugs—that either led to hospitalization (eight) or occurred during hospitalization (one), and received doses of IV-LEV of 150 mg/kg/day or greater, with a mean dose of 228 ± 48 mg/kg/day. Eight of nine children had resolution of the acute repetitive seizures. Seizure frequency was reduced to less than baseline in seven children (seizure-free in two, ≥80% reduction in four, and 50% reduction in one). Except for one child with increased seizures, IV-LEV was well tolerated in all children without complications.

KEY WORDS: Levetiracetam, Intravenous, Intractable epilepsy, Children, High-dose.

Levetiracetam (LEV) has been proven effective and well tolerated in prospective and retrospective studies in children with refractory generalized and/or partial seizures (Opp et al., 2005; Glauser et al., 2006; Grosso et al., 2007; Khurana et al., 2007).

LEV has favorable pharmacokinetics, with rapid and complete absorption after oral administration, linear pharmacokinetics, low plasma protein binding, and low potential for drug interactions (Patsalos, 2004; Ramael et al., 2006). Intravenous LEV (IV-LEV) is well tolerated in adults, has a pharmacokinetic profile consistent with oral LEV (Ramael et al., 2006; Baulac et al., 2007), is a safe and effective alternative to oral LEV when oral administration is not possible (Baulac et al., 2007), and has been effective in benzodiazepine-refractory status epilepticus (Knake et al., 2008). The safety and efficacy of IV-LEV has also been demonstrated in children (Goraya et al., 2008).

The typical maintenance dose of LEV is 40–60 mg/kg/day; however, clearance of LEV in young children is 30–40% greater (Pellock et al., 2001) than in adults. Higher doses of LEV may be necessary to demonstrate an obvious effect in children. In one child, oral LEV was tolerated and very effective at 120 mg/kg/day, suggesting that higher doses may benefit some children (Mandelbaum et al., 2005).

We report our experience with high-dose IV-LEV for acute seizure exacerbations, mainly acute repetitive seizures, in young children with medically intractable epilepsy.

Methods

Medical records of nine consecutive children (two boys and seven girls, mean age 2.0 ± 1.2 years, from September 2006 to June 2007) hospitalized with an exacerbation of medically intractable epilepsy treated with high-dose IV-LEV, were retrospectively reviewed. Seizure exacerbation was defined as having multiple seizures per day, with a greater than 2-fold increase in seizure frequency compared to baseline. One child had refractory status epilepticus and three had multiple seizures per hour. This study was approved by the Children's Hospital, Boston Institutional Review Board.

In previous reports, LEV had been used at up to 115–120 mg/kg/day (Mandelbaum et al., 2005; Goraya et al., 2008) with reported good efficacy, so we studied children

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taking 150 mg/kg/day or more. Only two of the nine children were taking oral LEV when they received IV-LEV (patient 3: 1,500 mg/day, increased to 2,000 mg/day; patient 9: 1,600 mg/day, increased to 3,300 mg/day).

For the seven children not taking oral LEV, IV-LEV was started at 30 mg/kg every 8 hours on day 1 (90 mg/kg/day), and was changed to every 6 hours on day 2 (120 mg/kg/day), and every 4 hours on day 3 (180 mg/kg/day), while continuing each dose at 30 mg/kg. IV-LEV was carefully titrated, with close monitoring of seizures and vital signs using video–electroencephalography (v-EEG) telemetry and cardiorespiratory monitoring. If no systemic adverse reactions were observed, IV-LEV was further titrated up to the dose optimal for seizure control, continuing every 4 hours, but increasing each dose from day 4. When children were able to take oral medications, IV-LEV was converted to equivalent oral daily doses, after stabilizing on optimal doses for seizure control for more than 1 day. For two children already treated with oral LEV, IV-LEV was given at the same total dose per day, but divided into every 6 hours dosing, and each dose was increased to obtain optimal seizure control, while being followed with similar monitoring.

Children were discharged home on oral LEV at the maximum daily dose listed in Table 1, except for the one child with increased seizures in whom LEV was rapidly discontinued.

Results

The clinical features are summarized in Table 2, and the effects of high-dose IV-LEV on seizure frequency and adverse reactions are summarized in Table 1. Mean dose of IV-LEV was 228 ± 48 mg/kg/day. Various seizures types were seen (complex partial seizures in six, tonic seizures in three, tonic–clonic seizures in one, atypical absence seizures in one, and drop seizures in one). Etiology of epilepsy was symptomatic in eight: malformations of cortical development (four), genetic abnormality (two), other syndromes (one), and mitochondrial disorder (one). Eight of nine children had resolution of the acute repetitive seizures. Seizure frequency was reduced to less than baseline in seven children (seizure-free in two, ≥80% reduction in four, and 50% reduction in one). One child had resolution of acute repetitive seizures and returned to baseline seizure frequency, and seizures increased with higher LEV doses in another child. Except for the child with increased seizures, all others tolerated IV-LEV well without complications, such as agitation, behavioral changes, or somnolence.

Volume of distribution was calculated for patient 1 (0.9 L/kg), patient 2 (0.8 L/kg), and patient 3 (0.6 L/kg), but was not obtained for the other six patients. No immediate effects on seizures or EEG were seen following each IV-LEV dose, but a gradual change in seizure frequency was seen.

Discussion

We successfully used high-dose IV-LEV to reduce seizure frequency and control acute repetitive seizures in eight of nine children, a few of whom had been previously treated with "standard recommended doses" of up to 60 mg/kg/day without significant benefit. These children had failed other standard treatments for acute seizure exacerbation, including regular doses of lorazepam or diazepam, phenobarbital, or phenytoin. Medications used prior to high-dose LEV are listed in Table 2. One child had also failed pharmacologically induced coma with pentobarbital (patient 1). For all children, the decision to use high-dose IV-LEV was individually made in order to optimize seizure control when a trend for seizure improvement was seen at lower doses (the typical dose or moderately increased doses), while carefully

Table 1. Effects of high-dose intravenous levetiracetam (IV-LEV)

Pt	Weight	LEV max dose (mg/day)	LEV max dose (mg/kg/day)	LEV max level (trough)	Seizure frequency baseline	Seizure frequency before IV-LEV (acute exacerbation)	Resolution of SE/clusters	Seizure frequency on high dose IV-LEV	Overall effect
1	13 kg	3,300	254	82	100/day	Refractory SE	Yes	10–15/day	Refractory SE resolved, >80% seizure reduction
2	11 kg	3,000	272	45	4–5/month	15/day	Yes	1/week	>90% seizure reduction
3	11.8 kg	2,000	169	35	2–3/week	6–7/day	Yes	3–5/day	90% seizure reduction
4	10.5 kg	3,000	286	108	40/day	>1,000/day (40–50/hour)	Yes	None	Seizure-free
5	8 kg	1,200	150	44	6/day	11/day	Yes	1–2/day	>50% seizure reduction
6	8 kg	1,800	225	94	22/day	100–400/day (6–16/hour)	Yes	2/month	>90% seizure reduction
7	12.7 kg	2,800	220	156	3/day	>400/day (>20/hour)	Yes	None	Seizure-free
8	10 kg	2,000	200	N/A	3/day	6/day	No	30/day	Seizures worse
9	12 kg	3,300	275	54	7–15/day	40/day	Yes	7–15/day	No change compared to baseline, but resolution of clusters

LEV, levetiracetam; N/A, not applicable; SE status epilepticus.

Table 2. Clinical features

Pt	Age	Gender	Etiology	MRI	Exam	Seizure type	Interictal EEG	Ictal EEG	Other AEDs
1	3.5 years	F	Cortical dysplasia	L parietal dysplasia	R hemiparesis	Drop, CPS	Multifocal spikes	Generalized SW, runs of theta activity	VGB, VPA, ZNS, Pb, PHT, CLZP, DZP
2	1.5 years	F	Mitochondrial disorder	Normal	Diffuse hypotonia	CPS	Occipital spikes	L and R temporal onset	Pb, TPM, OXC, ZNS, CLZP, LTG
3	2.5 years	M	3C syndrome (Ritscher-Schinzel syndrome)	Dandy Walker malformation, volume loss	Diffuse hypotonia	CPS	Multifocal spikes	L temporal onset	Pb, CLZP, GBP
4	2.5 years	F	SMEI (SCN1A mutation)	Normal	Mild diffuse hypotonia	Atypical Absence	Irregular generalized SW	Generalized SW	Pb, ZNS, VPA, CLZP
5	3 month	F	Bilateral Polymicrogyria	Bilateral Polymicrogyria	Diffuse hypotonia	CPS	Multifocal spikes, max R frontocentral	R frontocentral slow, decrement then build up in R temporal area	Pb, PHT, OXC, ZNS
6	8 month	M	Cryptogenic	Normal	Diffuse hypotonia	Tonic, CPS	Multifocal spikes	L and R temporal onset	Pb, Vitamin B6
7	3.7 years	F	4p- syndrome (Wolf-Hirschhorn syndrome)	Microcephaly, delayed myelination, small brainstem, thin corpus callosum	Diffuse hypotonia	Tonic–clonic, Myoclonic	R temporal parietal occipital spikes	3.5 Hz SW with posterior predominance	TPM, Pb
8	1.5 years	F	Idiopathic	Normal	Normal	CPS	L fronto-centrotemporal spikes	L temporal onset	OXC, Pb, VPA
9	2 years	F	Cortical dysplasia	R frontal dysplasia	Diffuse hypotonia	Tonic	Multifocal spikes	Generalized electrodecrement	TPM, LTG

M, male; F, female; SMEI, severe myoclonic epilepsy of infancy; L, left; R, right; CPS, complex partial seizure; SW, spike and wave complexes; CLZP, clonazepam; DZP, diazepam; GBP, gabapentin; LTG, lamotrigine; OXC, oxcarbazepine; Pb, phenobarbital; PHT, phenytoin; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.

monitoring for adverse reactions. Acute intervention was medically necessary for the significant seizure exacerbation, with rapid titration of LEV to optimize seizure control within a short period of time.

In selected infants and children with an exacerbation of medically intractable epilepsy, with acute repetitive seizures, a larger dose of LEV may be required to achieve the desired effect. Interestingly, many of our studied children had previously received LEV at standard recommended doses (up to 30 mg/kg/day), but had no obvious efficacy. Lack of response may have been from the drug resistance in the child, or difference in pharmacokinetics. Mean half-life ($T_{1/2}$) of LEV is shorter in infants and young children (Pellock et al., 2001; Glauser et al., 2007), and LEV clearance is more rapid (Pellock et al., 2001). Elimination $T_{1/2}$ on LEV in this age group (5.3 h) was slightly shorter than that reported for children aged 6–12 years (6 h), and shorter than that reported for adults (6–8 h) (Glauser et al., 2007). For three of our nine patients, volume of distribution was obtained, which ranged from 0.6–0.9 L/kg, similar to previously reported values (Pellock et al., 2001).

Regardless of mechanism, our children required significantly higher doses of IV-LEV with rapid titration to achieve a response to IV-LEV. Such high doses were justified by medical necessity in those with a partial clinical response to the more standard doses, and would not have been used if optimal seizure control had been achieved at the lower doses.

Short-term IV-LEV has been well tolerated in adults (Baulac et al., 2007) and children (Goraya et al., 2008), after switching from an oral dose, All our children on high-dose IV-LEV were later converted to equivalent oral doses of LEV without complications.

LEV has been well-tolerated, and is relatively safe. Except for the one child with increased seizures, no significant short-term side effects were seen in our children (who received a mean dose of 228 ± 48 mg/kg/day) including behavioral side effects. Regarding tolerability, LEV has been reported as well tolerated at doses up to 115–227 mg/kg/day, without observed adverse effects (Mandelbaum et al., 2005; Goraya et al., 2008); in previous studies, somnolence and irritability were the most common side effects, which were relatively mild and transient (Mandelbaum et al., 2005; Grosso et al., 2007). Long-term side effects of this high-dose have not been assessed, and close follow-up will be necessary for such assessment.

Conclusion

High-dose IV-LEV appears to be well tolerated and effective for treating acute seizure exacerbations. Higher doses of LEV may be necessary to achieve efficacy in certain children with exacerbation of medically intractable epilepsy, with acute repetitive seizures. Further studies are necessary to confirm such effects. LEV has a favorable side-effect profile, with no known life-threatening side-effects; however, the long-term safety of this high-dose has not been assessed and needs careful evaluation in future studies.

Acknowledgments

The study was presented in December 2007, at the Annual meeting of the American Epilepsy Society in Philadelphia, Pennsylvania, U.S.A.

Disclosure

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors has any conflict of interest to disclose.

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