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Levetiracetam for Treatment of Neonatal Seizures

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Abstract

Neonatal seizures are often refractory to treatment with initial antiseizure medications. Consequently, clinicians turn to alternatives such as levetiracetam, despite the lack of published data regarding its safety, tolerability, or efficacy in the neonatal population. We report a retrospectively identified cohort of 23 neonates with electroencephalographically confirmed seizures who received levetiracetam. Levetiracetam was considered effective if administration was associated with a greater than 50% seizure reduction within 24 hours. Levetiracetam was initiated at a mean conceptional age of 41 weeks. The mean initial dose was 16 ± 6 mg/kg and the mean maximum dose was 45 ± 19 mg/kg/day. No respiratory or cardiovascular adverse effects were reported or detected. Levetiracetam was associated with a greater than 50% seizure reduction in 35% (8 of 23), including seizure termination in 7. Further study is warranted to determine optimal levetiracetam dosing in neonates and to compare efficacy with other antiseizure medications.

Keywords

neonatal seizures; status epilepticus; levetiracetam; anticonvulsant

Neonatal seizures occur in 1 per 1000 births¹ and may adversely impact neurodevelopmental outcome.² No class A evidence-based guidelines currently exist for the pharmacologic treatment of neonatal seizures,³⁻⁵ and management is highly varied.⁶ Phenobarbital is the most commonly administered antiseizure medication in the neonatal period,^{6,7} but results in complete termination of electroencephalographically confirmed seizures in less than half of patients when used as a first line medication.⁸ Other first line medications such as phenytoin and the benzodiazepines are also incompletely efficacious, prompting clinicians to utilize a variety of other antiseizure medication with minimal supporting evidence of safety, tolerability, and efficacy in neonates.⁹⁻¹³

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Author Contributions

NA wrote the first draft. All authors contributed to study design, data analysis, and manuscript preparation. HM participated in subject identification. NA and AG-C participated in data collection.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

Ethical Approval

The study was approved by the hospital's Institutional Review Board.

Levetiracetam is an antiepileptic drug frequently used in chronic epilepsy management and is approved by the US Food and Drug Administration (FDA) in children older than 4 years. It may also have a role in the management of acute symptomatic seizures and status epilepticus in older pediatric^{9,10,13-19} and adult²⁰⁻²⁵ populations. Randomized controlled trials have not evaluated the use of levetiracetam in critically ill pediatric patients, including neonates, but levetiracetam is commonly used off-label for neonatal seizures.²⁶ Levetiracetam can easily be administered to neonates because of the oral solution and intravenous formulations. Furthermore, it has little serum protein binding, is not hepatically metabolized, creates no drug-to-drug interactions, and levetiracetam has few known serious adverse side effects, in contrast to other antiseizure medications, which may cause cardiopulmonary depression, arrhythmia, and coagulopathy. These features suggest that levetiracetam could be safe and efficacious in treating neonatal seizures, but neonatal data are needed. We describe the safety, tolerability, and efficacy of levetiracetam in a retrospective cohort of consecutive neonates with electroencephalographically confirmed seizures.

Methods

This is a retrospective cohort study of consecutive neonates with electrographically confirmed seizures who received intravenous levetiracetam for electro-clinical or electrographic-only (subclinical or nonconvulsive) seizures in the Newborn Infant Intensive Care Unit of The Children's Hospital of Philadelphia during a 1-year period (October 2008-October 2009).

Neonates who received levetiracetam were identified by a search of the electronic pharmacy database. Clinical data were obtained from review of electronic hospital records and rereview of electroencephalographic recordings. Data gathered include the following: (1) patient demographics (pregnancy and birth history, gestational age, postnatal age, and neonatal seizure etiology); (2) current medical issues (including neurologic and medical conditions, cardiorespiratory status, and renal function); (3) seizure types (for those with electroclinical seizures); (4) electrographic seizure duration; and (5) antiseizure medication administration including the sequence of drugs, timing, dosing, duration of therapy, and relationship to encephalographic seizure reduction. Per our clinical practice protocol, all neonates with seizures undergo continuous cardiopulmonary monitoring and long-term video-encephalographic monitoring, usually continuing for 24 hours after seizure cessation.

Neonates received initial intravenous levetiracetam bolus doses of 10 to 20 mg/kg. In the absence of strong safety data in neonates at the time levetiracetam was introduced to the Neonatal Intensive Care Unit of The Children's Hospital of Philadelphia, this loading dose was chosen by an institutional drug use evaluation committee based on standard outpatient starting doses. After initial loading, levetiracetam was administered twice per day. Current manufacturer recommendations state that the medication should be diluted in 100 mL of diluent; however, administration of this large volume may be impractical in neonates and concentrations as high as 50 mg/mL have been well tolerated in the pediatric population.²⁷ All bolus and maintenance doses were diluted with normal saline to a concentration of 20 mg/mL. The exact volume depended on the dosing (mg/kg) and patient weight. For example, a 4-kg neonate administered 15 mg/kg would receive a 3 mL bolus. Boluses were administered over 15 minutes. Serum levels of levetiracetam were not obtained in most patients.

Cardiopulmonary adverse effects were considered present if within 2 hours of levetiracetam administration vital sign flow sheets or care notes documented desaturation, reduced respiratory rate, increased ventilator support requirement, arrhythmias, blood pressure, or

heart rate increase or decrease by more than 10% compared to the prior 2 hours, or if vasopressors were initiated or increased. Levetiracetam was considered effective if administration was associated with a greater than 50% reduction in electrographic seizures within 24 hours of treatment initiation. The pre-levetiracetam time period varied in duration across subjects based on the time to seizure detection, speed of overall management, and the number of antiseizure medication utilized before levetiracetam.

Results

A total of 23 neonates (11 males and 12 females) received levetiracetam during the 1-year study period (Table 1). Their mean gestational age was 38.7 ± 1.7 weeks (range, 35-41 weeks). Levetiracetam was administered at a mean conceptional age of 40.7 ± 1.5 weeks (range, 38-42 weeks), which corresponded to a mean postnatal age of 14 ± 13 days (range, 0-41 days). The etiologies for their neonatal seizures were hypoxic-ischemic encephalopathy (8), presumed genetic/metabolic disorders (4), brain malformations (3), central nervous system infections (3), stroke (2), cryptogenic seizures (2), and tumor (1). Clinical seizure types included focal or multifocal clonic or tonic (18), subtle seizures (5), and desaturation/apnea (2). Electrographic-only (nonconvulsive) seizures occurred in 13 neonates, and 10 of these had almost all electrographic-only seizures with very few associated with any clinical change. In all, 12 were reported as electro-graphic status epilepticus.

Levetiracetam was administered as a first-line antiseizure medication in 4 neonates (17%), second-line in 14 neonates (61%), and third-line or later in 5 neonates (22%). All subjects who received levetiracetam as a second-line medication had received phenobarbital as the first line therapy. Neonates who received levetiracetam as a third-line or later antiseizure medication were administered phenobarbital and phenytoin prior to levetiracetam. The mean initial dose was 16 ± 6 mg/kg (range, 5-22 mg/kg) and the mean maximum dose was 45 ± 19 mg/kg/day (range, 10-80 mg/kg/day).

No serious cardiopulmonary adverse effects were identified. No patient was discontinued from levetiracetam because of serious or intolerable adverse effects.

Levetiracetam was associated with seizure improvement within 24 hours in 8 of 23 neonates (35%), including termination in 7 of 8 (88%) and reduction by >50% in 1 of 8 (12%). Of the 8 subjects who benefited, levetiracetam was administered as a first-line antiseizure medication in 1 neonate, second-line antiseizure medication in 5 neonates, and third-line antiseizure medication in 2 neonates. Four patients (17%) had improvement within 24 to 72 hours of levetiracetam initiation, including termination in 2 (50%) and reduction by >50% in 2 (50%). There was no seizure reduction in 8 of 23 (35%). The impact could not be evaluated in 3 of 23 subjects (13%) because they received levetiracetam after seizures had already terminated. The maximum mean daily dose administered was not significantly different in neonates with and without benefit (40 ± 12 mg/kg/day vs 48 ± 20 mg/kg/day, unpaired *t* test *P* = .78).

Of the 21 patients who survived to discharge, 17 were discharged on levetiracetam (81%). These included 8 of 8 with seizure termination or reduction within 24 hours (5 on only levetiracetam and 3 on levetiracetam and phenobarbital), 8 of the 12 without benefit within 24 hours (0 on only levetiracetam, 5 on levetiracetam and phenobarbital, and 3 on levetiracetam, phenobarbital, and also topiramate or phenytoin), and 1 of the 3 without evaluable effect (only levetiracetam).

Discussion

Survey data suggest that levetiracetam is commonly recommended by pediatric neurologists managing neonatal seizures,²⁶ despite a paucity of data regarding safety, tolerability, and efficacy. Our retrospective cohort study of 23 neonates with electro-graphically confirmed seizures did not identify any serious adverse cardiopulmonary effects, and levetiracetam was not discontinued in any neonates because of serious adverse events. Levetiracetam was associated with greater than 50% seizure reduction within 24 hours of treatment initiation in 35% of neonates. Of those who benefited, 88% were rendered seizure free.

Levetiracetam's pharmacokinetic profile suggests it could be a useful medication in critically ill neonates with seizures. Neonates have lower serum protein values compared to adults, placing them at an increased risk for toxicity secondary to elevated free drug concentrations of highly protein bound antiseizure medications such as phenytoin, and levetiracetam has minimal protein binding. Furthermore, critically ill neonates with seizures are often receiving polypharmacy and, in contrast to other intravenous antiseizure medications, levetiracetam has no cytochrome P450 drug-drug interactions. Clinical seizure types observed in our retrospective study included focal or multifocal clonic or tonic, and subtle seizures. Levetiracetam is approved by the FDA for use in partial onset seizures, juvenile myoclonic epilepsy, myoclonic seizures, and primary generalized tonic clonic seizures, suggesting the potential for benefit in neonates with the types of seizures occurring in our cohort. Finally, in epileptic children, interictal intravenous levetiracetam boluses of up to 60 mg/kg administered over 5 to 6 minutes achieved serum levels of more than 100 mg/ml and resulted in no significant changes in blood pressure, electrocardiographic abnormalities, or local infusion site reactions.²⁷ The observation that intravenous levetiracetam can be delivered quickly and achieve high serum levels suggests a possible role for levetiracetam in the management of acute seizures.

Case series and case reports have described tolerability and possible efficacy of levetiracetam for neonatal seizures, including 2 neonates with seizure administered oral levetiracetam,⁹ a neonate with intractable malignant migrating partial seizures,¹⁰ as a prophylactic antiseizure medication in a neonate with presumed acute symptomatic seizures because of leukemia.¹² Slightly more data are available in infants. A case series of 11 children aged 2 days to 9 years with refractory status epilepticus treated with levetiracetam doses of 15 to 70 mg/kg (intravenous in 6, nasogastric in 5) did not result in adverse effects. A total of 5 children, all of whom had received at least 30 mg/kg/ day, had some benefit in a median of 1.5 days.¹³ Another case series of 28 children under the age of 2 years included some neonates (minimum age 2 weeks) and reported that with a 6.3-month mean duration of treatment, levetiracetam reduced seizures in 54%, including 14% with seizure freedom.¹¹ However, data were not available for the individual neonates. Our data describing a larger consecutive cohort of neonates treated with levetiracetam substantially expands the reported clinical experience with levetiracetam in neonates.

Although there have been no prospective studies comparing levetiracetam to other antiseizure medications, a growing number of retrospective, single-center, open-label case series and case reports have provided additional evidence that levetiracetam may be safe and effective for treating status epilepticus and acute repetitive seizures in nonneonatal children. One series described 32 children treated with intravenous levetiracetam (50 mg/kg over 15 minutes) for acute seizures or status epilepticus and reported that all patients had seizure termination within 25 to 30 minutes of infusion.¹⁷ A second series reported that intravenous levetiracetam loading doses of 6.5 to 31 mg/kg terminated nonconvulsive status epilepticus in 2 of 2, acute repetitive seizures in 4 of 4, and resulted in temporary seizure termination in 3 with refractory status epilepticus.¹⁴ A third series reported 10 children who received

intravenous levetiracetam and described status epilepticus termination in 1, status epilepticus improvement in 1, and acute repetitive seizure termination in 2.¹⁶ Finally, 2 infants with migrating partial seizures of infancy in refractory status epilepticus had seizure termination within 12 hours of 60 mg/kg intravenous levetiracetam loads.²⁸ None of these series described any adverse effects.^{14,16,17,28} Additional case reports have reported that levetiracetam resulted in improvement in nonconvulsive status epilepticus^{15,19,29} and myoclonic status epilepticus¹⁸ in children.

Our retrospective cohort study has multiple limitations. First, although no adverse cardiopulmonary events were identified, the retrospective nature of chart review limits firm conclusions about levetiracetam's safety and tolerability. While our safety profile was consistent with other studies of intravenous levetiracetam in critically ill children^{13,14,16,17} and larger studies of critically ill adults,^{20-22,24,25,30} there are rare reports of elevations in liver enzymes,²⁵ possible fulminant hepatic failure³¹ and thrombocytopenia.^{22,32} This study is too small to detect rare events and we did not perform extensive laboratory testing in a standardized manner. Second, dosing was not standardized, and it is unknown whether dosing was optimal as neonatal pharmacokinetic data are not available. A retrospective series of children with refractory epilepsy reported no correlation between plasma level and efficacy,³³ suggesting it may be difficult to identify an optimal dosing regimen. Third, while levetiracetam was associated with a greater than 50% reduction in seizures in 35% of neonates within 24 hours, this small retrospective uncontrolled study does not provide quality efficacy data and merely suggests future prospective study of levetiracetam effectiveness is warranted. Seizures because of acute encephalopathy are known to spontaneously cease over time. Given that levetiracetam was often used as a second or third line antiseizure medication, some of the association with seizure reduction, especially in the 4 neonates with improvement noted in 2 to 3 days, may have simply related to passage of time and not levetiracetam efficacy. Furthermore, because of variation in management, the duration of the pre-levetiracetam period used to calculate pre-levetiracetam seizure burden varied across subjects. Without a placebo group and standardized timing, it is not possible to determine whether some or all seizure improvement relates to the passage of time or levetiracetam administration.

Despite the limitations of this small retrospective observational study, the findings are in agreement with other smaller reported series and suggest that levetiracetam is safe and well-tolerated when administered to critically ill neonates. There is an association with seizure reduction or termination within 24 hours of administration, primarily when used as a second-line antiseizure medication. Additional, larger prospective studies are warranted to define the role of levetiracetam in the management of neonatal seizures. A dose finding study may be needed initially and must include data regarding serum levels of levetiracetam. In our cohort, dosing of 40 mg/kg/day was not associated with major adverse effects and none of the neonates who benefitted from levetiracetam discontinued the medication because of intolerability, so this may be a reasonable dose to study. Consistent with data regarding phenytoin and phenobarbital,⁸ levetiracetam administration was associated with seizure improvement in less than half of neonates, and this low but expected response rate has implications for sample size calculations in future prospective comparative studies.

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Summary of Subjects

Table 1

Subject	Sex	Gestational Age	Conceptional Age at Levetiracetam Administration	Etiology	Seizure Type	Encephalographic Features	Anticonvulsant Order	Initial Levetiracetam Dose (mg/kg)	Maximum Levetiracetam Dose (mg/kg/day)	Seizures After Levetiracetam Administration	Encephalographic Monitoring Duration (days)	Encephalographic Monitoring Duration After Seizures Terminated (hours)	Discharge Anticonvulsants
1	F	38	42	Genetic-metabolic	Focal myoclonic and tonic	Reactive, excess discontinuity, MF sharps, MF myoclonic, and tonic seizures	LEV	5	40	Terminated	1	24-36	LEV
2	M	41	43	Genetic-metabolic	Focal clonic and tonic	Reactive, continuous, excess MF sharps, MF clonic seizures	PB, LEV	13	40	Terminated	2	36-48	LEV, PB
3	F	38	39	Tumor	Subtle eye, mostly NCS	Reactive, excess discontinuity, MF sharps, MF NCSE	PB, PHT, LEV	19	61	Terminated	6	36-48	PB, LEV
4	F	FT	42	HIE	Focal clonic	Reactive, excess discontinuity, MF excess sharps, MF clonic, and NCS	PB, LEV	5	29	Terminated	6	36-48	PB, LEV
5	M	41	41	Stroke	Focal clonic	Reactive, excess discontinuity, focal sharps, no seizures	PB, PHT, LEV	18	38	Terminated	2	36-48	LEV
6	M	40	42	HIE	MF clonic	Reactive, excess discontinuity, MF sharps, MF clonic seizures	PB, LEV	20	40	Terminated	5	48-60	LEV
7	F	35	40	Infection	Focal clonic, subtle face, mostly NCS	Reactive, excess discontinuity, excess focal sharps, focal clonic seizures, and multifocal NCSE	PB, LEV	15	50	Terminated	2	24-36	LEV
8	F	39	39	HIE	Focal clonic, subtle face, mostly NCS	Un reactive, excess discontinuity and attenuated, excess MF sharps, MF NCSE	PB, LEV, PHT	20	20	Reduced seizures > 50%	4	NA	LEV
9	F	35	40	CNS malformation	MF tonic, desa/apnea, NCS	Reactive, excess discontinuity, excess MF sharps, MF tonic, and NCS	PB, LEV	10	70	Terminated in > 24 hours	3	12-24	PB, LEV
10	M	39	39	HIE	MF clonic, subtle face, mostly NCS	Unreactive, excess discontinuity, excess MF sharps, MF clonic, and NCSE	PB, LEV	20	40	Terminated in > 24 hours	4	48-60	PB, LEV

Subject	Sex	Gestational Age	Conceptional Age at Levetiracetam Administration	Etiology	Seizure Type	Encephalographic Features	Anticonvulsant Order	Initial Levetiracetam Dose (mg/kg)	Maximum Dose (mg/kg/day)	Seizures After Levetiracetam Administration	Encephalographic Monitoring Duration (days)	Encephalographic Monitoring Duration After Seizures Terminated (hours)	Discharge Anticonvulsants
11	F	37	38	CNS malformation	MF clonic, mostly NCS	Reactive, excess discontinuity, excess MF sharps, MF clonic, and NCSE	PB, PHT, LEV, TPM	19	80	Improvement in > 24 hours	2	NA	LEV, PB
12	M	40	40	HIE	MF clonic and tonic, mostly NCS	Reactive, excess discontinuity, excess MF sharps, MF clonic, and NCSE	PB, LEV	19	63	Improvement in > 24 hours	6	NA	PB, LEV
13	F	39	39	CNS malformation	MF tonic and clonic, NCS	Excess discontinuity, MF sharps, multifocal tonic and clonic seizures, multifocal NCS	PB, PHT, TPM, LEV	20	22	No improvement	4	NA	LEV, TMP, PB
14	M	41	41	HIE	Focal tonic and clonic, mostly NCS	Unreactive, excess discontinuity, excess MF sharps, MF clonic, and NCSE	PB, LEV, PHT, MDZ	18	53	No improvement	4	NA	PB, PHT
15	M	39	42	Cryptogenic seizures	Focal clonic	Reactive, excess discontinuity, excess MF sharps, focal clonic seizures	PB, LEV, TPM	20	64	No improvement	2	NA	PB, LEV, TMP
16	M	39	41	Infection	NCS	Unreactive, excess discontinuity progressing to attenuated and featureless, focal NCSE	LEV, PB	21	61	No improvement.	2	NA	PB, LEV
17	M	39	41	Cryptogenic seizures	MF clonic, subtle, apnea/desat, NCS	Reactive, excess discontinuity, excess MF sharps, MF clonic, and NCS	PHT, PB, LEV, LZP, TPM, B6, FA	19	55	No improvement	3	NA	PHT, TMP, PB
18	F	40	40	HIE	Subtle face/eye, mostly NCS	Reactive, excess discontinuity, MF sharps, MF NCSE	PB, LEV, PHT	20	40	No improvement.	3	NA	Died
19	F	38	42	Infection	MF clonic, mostly NCS	Unreactive, highly attenuated and featureless, MF NCSE	PB, LEV, PHT	21	21	No improvement.	2	NA	Died
20	F	41	41	Stroke	Desaturation, subtle face, mostly NCS	Reactive, mild excess discontinuity, focal excess sharps, focal clonic, and NCSE	PB, LEV, PHT, TPM	22	65	No improvement.	4	NA	LEV, PB, TPM, PHT
21	M	37	38	HIE	Focal clonic	Unreactive, excess discontinuity and attenuated, no seizures	PB, LEV	8	25	Unable to judge	2	NA	Died

Subject	Sex	Gestational Age	Conceptional Age at Levetiracetam Administration	Etiology	Seizure Type	Encephalographic Features	Anticonvulsant Order	Initial Levetiracetam Dose (mg/kg)	Maximum Dose Levetiracetam (mg/kg/day)	Seizures After Levetiracetam Administration	Encephalographic Monitoring Duration (days)	Encephalographic Monitoring Duration After Seizures Terminated (hours)	Discharge Anticonvulsants
22	M	38	42	Genetic-metabolic	Subtle extremities	Reactive, mild excess discontinuity, no shaps, no seizures	LEV, PB	5	10	Unable to judge	2	NA	None
23	F	38	43	Genetic-metabolic	Focal clonic	Burst-suppression evolved to hypsarrhythmia, no seizures	LEV, PB, PHT, B6, FA, TPM	15	57	Unable to judge	1	NA	LEV

Abbreviations: FA, folinic acid; FT, full term; GA, gestational age; HIE, hypoxic ischemic encephalopathy; LEV, levetiracetam; NA, not-applicable since seizures did not terminate; MDZ, midazolam; MF, multifocal; NCS, nonconvulsive seizures; NCSE, nonconvulsive status epilepticus; PB, phenobarbital; PHT, phenytoin; TPM, topiramate.