

Observational Study

Response of levetiracetam in neonatal seizures

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Abstract

AIM: To review the clinical response to levetiracetam (LEV) in neonatal seizure management in intensive care unit.

METHODS: Medical records of neonates who received LEV from January 2009 to August 2014 were reviewed. Their demographic data, clinical characteristics, etiology, seizures, electroencephalograms, response to treatment and outcome were noted. Literature review of use of LEV in neonates were also performed *via* PubMed and EMBASE with keywords - "neonates", "seizures", "epilepsy" and "LEV" up to Sep 2014 and retrieved the publications. The response rate to LEV was compared.

RESULTS: Twelve neonates were identified during the study period. All patients received phenobarbitone loading prior to consideration of LEV. Seven (58%) and nine (75%) achieved seizure freedom 24 h and 72 h after LEV was added, both clinically and electrographically. No serious adverse effects were associated with LEV use. From the literature, there are total 144 neonates reported to have used LEV. The overall results suggested that LEV could control up to 90% of neonatal seizures.

CONCLUSION: LEV was found to be relatively safe and efficacious in treating neonatal seizures, but might not work well in the most severe hypoxic ischemic encephalopathy.

Key words: Levetiracetam; Phenobarbitone; Neonates; Seizures

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Core tip: Neonatal seizures are common, but there is lack of evidence to support use of anticonvulsants in this group of patients. Phenobarbitone remains the first line of treatment despite its limitations. The current study aims to review our experience of using levetiracetam (LEV) in management of neonatal seizures and to compare with the experience reported in the literature. We find that LEV is a relatively safe and feasible treatment option. Difficulties in performing studies were also discussed with the latest report of using bumetanide for treatment of neonatal seizures.

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INTRODUCTION

Seizures are common in the neonatal period. The incidence ranges from 2-4 in 1000 full term newborns and the prevalence is even higher in preterm babies. The etiologies are diverse, ranging from hypoxic-ischemic encephalopathy, encephalitis/meningitis, intraventricular hemorrhage, structural malformations, and metabolic or electrolyte disorders, *etc.* Phenobarbitone has been used since 1914 as the preferred first-line anticonvulsant in neonates. However, it has less than 50% efficacy in controlling neonatal seizures^[1]. In animal models, phenobarbitone has been shown to cause neuronal apoptosis, and in toddlers and infants, it is associated with negative cognitive side effects^[2].

Levetiracetam (LEV) is a pyrrolidine derivative, which acts through binding to and modulation of the synaptic vesicle protein SV2A. It is well tolerated with little drug-to-drug interactions. The most reported adverse effects are sedation and behavioral changes. However, its uses in neonates are still under investigation. This article aims to report our experience of using LEV in our neonatal intensive care unit especially those with hypoxic ischemic encephalopathy and compare with the reported cases.

MATERIALS AND METHODS

Infants were eligible if they received their first dose of LEV within the first four weeks of life between January 2009 to August 2014. These neonates were identified *via* the clinical data analysis and reporting system of the local health authority, which is an electronic database of the essential clinical information of all inpatients, including every single drug used. The medical records of all these infants were then retrieved. There was no loss of information in the records. Information on demographics (sex, gestational age, and Apgar score),

seizure onset, aetiology, neuroimaging, treatment, response and outcome were retrieved. The study was approved by the local clinical research ethics board (CREC 2014.072).

We then searched the PubMed and EMBASE in English with keywords - "neonates", "seizures", "epilepsy" and "LEV" up to Sep 2014 and retrieved the publications. Case series/reports with patients who started LEV in less than 28 d of life or less than 44 post-conceptual weeks were included.

RESULTS

The clinical characteristics of our patients are summarized in Table 1. There were six male and six female neonates identified during the study period. Gestational age ranged from 23 6/7 wk to 40 wk (mean: 34.9 wk, median 36 wk). One baby was extreme premature (less than 28 wk), five were premature neonates with gestational age between 28 to 36 wk and six were term babies. Etiologies of neonatal seizures include six neonates with hypoxic ischemic encephalopathy, three with meningitis/encephalitis, one had metabolic cause identified, one with presumed mitochondrial disease, and one had hypoglycemia whose seizures persisted even after hypoglycemia was corrected.

Utilization of LEV

All patients received phenobarbitone loading prior to consideration of LEV. LEV was offered if there was suboptimal response to initial anticonvulsants or if significant side effects were observed. All except one received intravenous LEV. The initial dosage ranged from 7.5-20 mg/kg, while the maintenance dosage ranged from 5-60 mg/kg per day. Seven (58%) and nine (75%) achieved seizure freedom 24 h and 72 h after LEV was added, both clinically and electrographically. We did not observe any cardiovascular complications (arrhythmia, hypotension), changes in blood counts, renal and liver function, *etc.*, after the introduction of LEV. Two babies died, one because of severe hypoxic ischemic encephalopathy and the other because of underlying metabolic disease. The remaining patients were discharged on LEV. Two patients were discharged with adjunctive phenobarbitone, while four were discharged with adjunctive topiramate as well. Six patients had discontinued LEV on subsequent follow up. The longest follow up was five years and five months.

DISCUSSION

There are various mechanisms that make the immature brain more excitable as compared to adult brain. These include overabundant excitatory glutamatergic neurons and paradoxical excitatory action of gamma-aminobutyric acid in the developing brain^[3]. Immature development of the neurotransmitter systems leads to difference in targets for conventional anticonvulsant to work. There is only one randomized controlled trial in

Table 1 Clinical characteristics of neonates receiving levetiracetam

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
Gestation (wk)	38	39	35	38	41	29	36	23.6/7	30	39	36	40
Apgar score (1 and 5 min)	9, 10	9, 10	9, 10	9, 10	8, 10	7, 9	0, 0	4, 6	0, 0	0, 0	0, 0	4, 7
Age of seizure onset (days of life)	19	10	8	1	1	0	0	3	0	0	0	0
Etiology	GBS meningitis	HSV encephalitis	Suspected mitochondrial	Hypoglycemia	Sulphite oxidase deficiency	<i>E. Coli</i> meningitis	HIE	HIE	HIE	HIE	HIE	HIE
Neuroimaging	Cystic encephalomalacia	Cystic encephalomalacia	Cystic encephalomalacia	Normal	Cystic encephalomalacia	Hydrocephalus with generalized atrophy	Cystic encephalomalacia	Cystic encephalomalacia	Peri-ventricular leukomalacia	Normal	Peri-ventricular leukomalacia	Diffuse cystic encephalomalacia
Electrographic seizures	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Clinical status epilepticus	No	No	No	No	No	Yes	No	No	No	No	No	Yes
Hypothermia	-	-	-	-	-	-	No	No	No	Yes	Yes	Yes
Anticonvulsant order	PHB/MDZ/LEV	PHB/LEV	PHB/LEV	PHB/LEV	PHB/LEV	PHB/MDZ/THI/LEV	PHB/MDZ/LEV	PHB/MDZ/LEV	PHB/MDZ/LEV	PHB/MDZ/LEV	PHB/MDZ/LEV	PHB/MDZ/LEV/THI
LEV loading dose (mg/kg)	15	20	10	7.5	10	10	15	16	18	10	8	20
Mm maintenance (mg/kg per day)	27	40	20	60	20	30	36	5	36	20	15	40
Seizure after 24 h	No	No	No	No	No	Yes	Yes	No	Yes	Yes	No	Yes
Seizure after 72 h	No	No	No	No	No	No	No	No	Yes	Yes	No	Yes
Anticonvulsant at discharge	LEV	TPM/LEV	PHB/LEV	PHB/LEV	Not applicable	TPM/LEV	Not applicable	LEV	LEV/TPM	LEV	PHB/LEV	PHB/LEV
Outcome	Mild delay	Severe delay	Severe delay	Normal	Death	Severe delay	Death	Severe delay	Moderate delay	Mild delay	Severe delay	Severe delay

GBS: Group B streptococcus; HSV: Herpes simplex virus; HIE: Hypoxic ischemic encephalopathy; PHB: Phenobarbitone; MDZ: Midazolam; LEV: Levetiracetam; THI: Thiopentone; TPM: Topiramate.

neonatal epilepsy in which Painter *et al.*^[1] studied the effect of phenobarbitone compared to phenytoin in a randomized crossover study. Their efficacies were similar: 43% vs 45% respectively. In our series, nine babies (75%) were seizure free within 72 h after LEV was added. But only 50% of babies with hypoxic ischemic encephalopathy had their seizures controlled after addition of LEV.

From the literature, (Table 2) there are total 144 neonates reported to have used LEV. They were heterogeneous in terms of etiology, treatment dosage and reported responses. Among these cases, up to 132 cases achieved seizure freedom, either immediately after loading dose or within 72 h. The overall results suggested that LEV could control up to 90% of neonatal seizures. In those studies with individual etiology specified, the overall seizure control rate is also lower, around 71%. The data in premature babies (defined as less than 37 gestation weeks) is encouraging. There have been 52 premature babies reported and 40 of them had seizures controlled after adding LEV (77%). But we have to bear in mind the potential problems of publication bias towards positive treatment responses.

The side effect profile of LEV is relatively mild and well tolerated. There may be nonspecific behavioral changes in up to 21% of children. Its uses in young children and acute repetitive seizure setting, even at high doses, were found to be relatively safe and effective^[15]. This is consistent with our observations and those reported in case series. In our series, all neonates were cared in the neonatal intensive care unit during the period of study with close hemodynamic monitoring. There was no immediate additional ventilator or inotropic support required after LEV was given. There were also no disturbances in the blood counts or liver and renal function. As most of these infants were critically ill with multiple medications, it would be preferable to use a drug with minimal drug-drug interaction, which is also a potential advantage of LEV. LEV might prevent intubation if anesthetic agents could be avoided for seizure control.

Interestingly, recently there have been animal studies regarding any possible neuroprotective or neurotoxic effect of LEV on neonatal rats. Griesmaier *et al.*^[16] found that LEV *per se* did not induce neurotoxicity in the developing rodent brain, but it increases brain injury in rodents with hypoxic-ischemic brain injury under the normothermic conditions, but not hypothermic conditions. But Komur *et al.*^[17] found that LEV has neuroprotective effect on hypoxic ischemic injury in neonatal rats. Further studies are

Table 2 Literature review of levetiracetam use in neonates

Ref.	Year of publication	No. of patients	Drugs used before LEV	Outcome: Seizure	No. of patients with HIE	Seizure outcome in HIE patients	Dosage (loading) (mg/kg)	Dosage (maintenance) (mg/kg per day)	Remarks
Shoemaker <i>et al.</i> ^[4]	2007	3	PHB/MIDZ/fPHT	All seizure free	1	Seizure controlled within 17 min of oral bolus	60 (oral)	30	
Fürwentsches <i>et al.</i> ^[5]	2010	6	PHB	All seizure free in 6 d	1	Seizure free	NA	10-50	Prospective
Ledet <i>et al.</i> ^[6]	2010	1	PHB	Seizure free	0	NA	NA	40	
Ramantani <i>et al.</i> ^[7]	2011	38	NA	30 seizure free at 1 wk	9	NA	10	45-60	Prospective
Khan <i>et al.</i> ^[8]	2011	22	PHB or PHT	19 seizure cessation at 1 h and 22 seizure free by 72 h	12	11 seizure cessation at 1 h			
Abend <i>et al.</i> ^[9]	2011	23	PHB or PHT	7 seizure terminated, 1 reduced seizure > 50%, 1 seizure terminated in > 24 h, 2 improvement in > 24 h, 8 no improvement, 1 unable to judge	8	2 seizure terminated, 2 reduced seizures > 50%, 1 improvement in > 24 h, 2 no improvement, 1 unable to judge	5-22	10-80	LEV as first drug in 4 cases
Aylward <i>et al.</i> ^[10]	2011	1	fPHT	Partially responsive	0	NA	20	19	
Sharpe <i>et al.</i> ^[11]	2012	18	PHB	6 seizure controlled	8	NA	20-40	5-10	
Rakshasbhuvankar <i>et al.</i> ^[12]	2013	8	PHB/PHT/MIDZ	6 "excellent", 1 partial, 1 ineffective	5	4 "excellent", 1 "partial"	5-10	10-35	
Khan <i>et al.</i> ^[13]	2013	12	PHB	9 seizure stopped in 24 h	5	3 seizure stopped in 24 h, 1 no response, 1 NA	25-50	50	
Kirmani ^[14]	2014	12	PHB	10 seizure free by 72 h	5	NA	25-50	25-50	

PHB: Phenobarbitone; PHT: Phenytoin; MIDZ: Midazolam; fPHT: Fosphenytoin; NA: Not available or applicable; HIE: Hypoxic ischemic encephalopathy; LEV: Levetiracetam.

needed to clarify the exact effect of LEV in neonatal brains, either in normothermic or hypothermic conditions and its clinical implications.

Up to date, the pharmacokinetics of LEV in neonates remains unclear. There is a wide range of dosing reported in the literature, ranging from 10-60 mg/kg loading and 10 to 80 mg/kg as maintenance and the frequency of dosing is also uncertain. We used a median dose of 12.5 mg/kg. Merhar *et al.*^[18] suggested that the half-life of LEV is 8.9 h, longer when compared to older children. But Sharpe *et al.*^[11] suggested that the clearance is higher in neonates suggesting more frequent dosing may be required. Therefore the optimal dosing and frequency of LEV in neonates still remains to be defined.

There were a few limitations to our study. This is a retrospective case series with relatively few patients. Together with published series/reports so far, could only provide level IV evidence to support use of LEV in neonates. But in real life practice, it is pragmatic to consider off-label use of drugs after gaining initial experience in older children. In fact, LEV is increasingly used in algorithms in the management of phenobarbitone-resistant neonatal seizures^[19].

Secondly, neonatal seizures were known to have spontaneous cessation, which could partially contributed to the observed efficacy of LEV. As most patients were already treated with multiple anticonvulsants prior to addition of LEV, the efficacy of LEV might be difficult to be delineated from the con-interventions.

Problems in studying medical treatment are best illustrated by the recent report of Ronit Pressler and members of the treatment of Neonatal seizures with Medication Off-patent consortium in using bumetanide for treatment of neonatal seizures^[20]. In the study, 30 patients were screened for electrographic seizures associated with hypoxic ischemic encephalopathy and 14 patients were enrolled. But five of them had no further seizures during the baseline period, so were de facto treatment failures. There are concerns and debates about what should be chosen and included in assessing the efficacy endpoints. It is controversial whether we should also include long-term developmental outcome and development of epilepsy, *etc.*, in the evaluation.

The experience from our case series, together with the published literature so far, supports LEV is a relatively safe and feasible option in neonatal seizures. But it may not work as well in neonates with most severe hypoxic ischemic encephalopathy. Further work is needed to evaluate its possible neuroprotective/neurotoxic effect in neonatal brains, the optimal dosage and role in neonatal seizures, *etc.*

COMMENTS

Background

Neonatal seizures are common, but there is lack of evidence to support use of anticonvulsants in this group of patients. Phenobarbitone remains the first line of treatment despite its limitations. Studies have reported the use of levetiracetam (LEV) in this group of patients.

Research frontiers

LEV is a broad-spectrum anticonvulsant which is licensed to be used in infants > 4 wk of age. Its use in neonates is still under investigation. It is very difficult to conduct controlled trials in neonatal seizures. The current research hotspot is to review our experience of using LEV in management of neonatal seizures and to compare with the experience reported in the literature.

Innovations and breakthroughs

This current study reviewed that LEV could be safely administered in sick neonates and its efficacy might be limited in those with most severe hypoxic ischemic encephalopathy. The experience from literature review also supports the relative safety of the drug.

Applications

LEV is a relatively safe and feasible treatment option for neonatal seizures.

Terminology

Neonatal seizures are common. The etiologies are diverse, ranging from hypoxic-ischemic encephalopathy, encephalitis/meningitis, intraventricular hemorrhage, structural malformations, and metabolic or electrolyte disorders, etc. LEV is a relatively safe and feasible treatment option for neonatal seizures.

Peer-review

Few medicines studied and approved to treat this subset of patients, management difficult.

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