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Levetiracetam: Safety and efficacy in neonatal seizures

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ABSTRACT

Purpose: Neonatal seizures are common, especially in prematurity. Phenobarbital (PB) currently represents the antiepileptic drug (AED) of choice, despite being related to increased neuronal apoptosis in animal models and cognitive impairment in human subjects. Levetiracetam (LEV) may have a more favorable profile since it does not cause neuronal apoptosis in infant rodents.

Methods: In a prospective feasibility study, LEV was applied as first-line treatment in 38 newborns with EEG-confirmed seizures, after ruling out hypoglycemia, hypocalcaemia, hypomagnesaemia and pyridoxin dependency. Initial intravenous doses of 10 mg/kg LEV were gradually increased to 30 mg/kg over 3 days with a further titration to 45–60 mg/kg at the end of the week. Acute intervention with up to 2 intravenous doses of PB 20 mg/kg was tolerated during LEV titration. LEV was switched to oral as soon as the infants' condition allowed. Based on clinical observation, EEG tracings (aEEG/routine EEGs), and lab data, drug safety and anticonvulsant efficacy were assessed over 12 months.

Results: In 19 newborns a single PB dose of 20 mg/kg was administered, while 3 newborns received 2 PB doses. 30 infants were seizure free under LEV at the end of the first week and 27 remained seizure free at four weeks, while EEGs markedly improved in 24 patients at 4 weeks. In 19 cases, LEV was discontinued after 2–4 weeks, while 7 infants received LEV up to 3 months. No severe adverse effects were observed.

Conclusions: These results illustrate the safety of LEV treatment in neonatal seizures, including prematurity and suggest LEV anticonvulsant efficacy. Additional PB treatment admittedly constitutes a methodological shortcoming due to the prolonged anticonvulsive efficacy of PB. Double blind prospective controlled studies and long-term evaluation of cognitive outcome are called for.

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1. Introduction

Neonatal seizures are the most frequent clinical manifestation of central nervous system dysfunction in the newborn, with an incidence of 1.5–3.5/1000 in term newborns and 10-130/1000 in preterm newborns.[1] Seizures in the newborn frequently signal significant brain pathology, such as hypoxic-ischemic injury, stroke, intracranial infection, hypoglycemia, inborn errors of metabolism, or brain malformations. Etiology significantly influences outcome. Newborn seizures correlate with higher mortality as well as motor or cognitive disability in survivors.[2,3] Furthermore, an association could be established between the amount of EEG seizure activity and subsequent mortality and morbidity in infants.[4] In this light, effective therapeutic interventions addressing both clinical seizures and EEG seizure activity might significantly improve neurocognitive development as well as reduce morbidity and mortality.

There are currently no evidence-based guidelines for evaluation and management of neonatal seizures. Available data indicate that phenobarbital (PB) remains the first-line treatment for neonatal seizures.[5] Yet, a recent Cochrane Review concluded that "there is little evidence to support the use of any of the anticonvulsants currently used in the neonatal period".[6] Conventional treatment (phenobarbital and phenytoin) only achieves clinical control in 50%–80% of cases and is even less effective in controlling most neonatal electroencephalographic seizures.[7] On the other hand, there is increasing concern over the long time adverse effects of phenobarbital, since it was shown to increase neuronal apoptosis in animal models[8] and induce cognitive impairment in infants and toddlers.[9]

Levetiracetam (LEV) is an effective and well-tolerated antiepileptic drug currently licensed as adjunctive therapy in the treatment of partial onset seizures with and without secondary generalization in adults, children and infants with epilepsy starting from 1 month of age (in oral application) and already licensed in children aged $\geq$4 years at study initiation.[10] Retrospective series in children including patients younger than 4 years showed comparable responder rates and side-effect profiles of add-on LEV treatment.[11,12] Prospective studies with small patient groups in infants and very young children reported similar results.[13,14] There are hardly any reports of severe, life threatening side effects, while most frequently observed adverse effects included somnolence and behavioral problems.[15] Furthermore, LEV presents a favorable profile regarding neuronal apoptosis: in contrast to most other established antiepileptic drugs it was not found to increase apoptosis in the developing rodent brain[16] or interfere with neuroprotective up-regulation of hypoxia inducible transcription factor 1 (HIF-1α)[17] and it was shown to decrease neurodegeneration in rodent models of hypoxia/ischemia[18] or epilepsy.[19,20]

To date, ten patients with neonatal seizures who were successfully treated with LEV in the neonatal period have been reported in detail,[21–23] while one of these patients received LEV intravenously.[21] The preliminary data on safety and anticonvulsive efficacy in the pilot study carried through at the University Hospital of Heidelberg in the years 2004–2006[23] encouraged us to further develop this protocol and initiate a prospective feasibility study in our institution.

This study analyses the results regarding anticonvulsant efficacy and treatment safety obtained using LEV in neonates with electroclinical and electrographic-only seizures. Our objectives were to evaluate 1) control of seizures, both clinically and electroencephalographically and 2) adverse effects associated with the intravenous or oral administration of LEV.

2. Methods

In 2006, following availability of intravenous LEV, consecutively admitted newborns with EEG-confirmed seizures, including premature and extremely premature infants treated at the Department of Neonatology and Pediatric Intensive Care of the University Hospital Carl Gustav Carus Dresden, Germany, were considered for this study. Infants presenting with clinical seizures that were confirmed as such through a clear correlation with pathologic EEG findings were subsequently treated with levetiracetam as a first-line AED.

Parents of newborns enrolled gave written informed consent for the study. In 15 cases, parents refused participation or enrollment was impracticable because of time limitations. In further 2 cases an underlying disease of complex genetic/metabolic origin was presumed that led to exclusion. These newborns were lost to the study and consequently received conventional PB treatment.

Neonatal seizures were defined according to Volpe's classification as subtle, focal clonic, multifocal clonic, focal tonic, generalized tonic and myoclonic. Infants that presented with subtle seizures, especially in the form of apneas, posed a major diagnostic challenge in prematurity. However, most of these patients showed multiple seizure types that altogether clinically confirmed the classification of events as epileptic.

The EEG recordings were performed bedside in the neonatal/intensive care unit; 10 or 21 cerebral electrodes, depending on the infant's head size (21 being applicable only to full-term eutrophic newborns), were applied according to the 10–20 International System, and EKG, EOG, chin EMG activity, abdominal respiration were the other parameters most frequently monitored. Tests were continued until a complete cycle of awake, quiet and active sleep states were recorded. EEG was monitored online and whenever state changes were not clearly distinguishable, recording was performed for at least 60 min. The EEG recording was routinely performed within 1–2 h from the clinical episode and reported by an experienced neonatologist/pediatric neurologist. EEGs were scored with an emphasis on age-dependent background activity[24]: 1. Normal/Mild abnormalities: normal pattern for gestational age, including slightly abnormal activity, e.g. mild asymmetry, mild voltage depression; moderate abnormalities: discontinuous activity with interburst interval too long for GA, clear asymmetry or asynchrony, absence of age-appropriate EEG features; 2. Major abnormalities: severe discontinuity in EEG for gestational age, burst suppression pattern, no appropriate wake–sleep cycle for gestational age, multifocal sharp waves; 3. Severe abnormalities: severe discontinuity in EEG for gestational age, burst suppression pattern, no appropriate wake–sleep cycle for gestational age, multifocal sharp waves.

The neurophysiology technologist performing the recording noted all behavioral changes or specific clinical correlates.

In 19 cases, an ictal pattern could be confirmed in the conventional EEG recording, while in another 9 cases, aEEG over 24–48 h presented typical seizure patterns. All other newborns enrolled had overtly pathologic interictal findings in conventional EEG pointing to a low seizure threshold. EEG recordings were not strictly classified according to the amount of epileptiform activity i.e. according to the relative density of spikes in a set period, due to the nature of newborn EEG; physiological background varies from burst suppression patterns to temporal spiking, according to gestational age. In this light, we chose to classify EEG data based on the deviation from the gestational-age appropriate norm. On the other hand, aEEG recordings were not included in this classification, since they were not applied routinely to every patient but rather used as a low-resolution longitudinal observation in order to clarify the nature of an event or series of events.

In EEG-confirmed newborn seizures, metabolic derangements (hypoglycemia, hypocalcaemia, hypomagnesaemia) were swiftly ruled out (glucose, electrolyte and blood gas screening available directly at the ward) and Vitamin B6 (100 mg i.v. up to a cumulative dosage of 300 mg i.v.) was administered. In case of ongoing seizures, LEV was administered as the first AED within the first 8 h from seizure manifestation, in some cases even as an acute intervention during a prolonged clinical seizure/EEG ictal pattern.

LEV initial dosage was 10 mg/kg intravenously administered twice daily increasing by 10 mg/kg over 3 days up to 30 mg/kg, while a further increase up to 45–60 mg/kg was performed at the end of the first week of treatment in case of persistent seizures or grave EEG pathology suggesting a low seizure threshold. Two single intravenous doses of PB 20 mg/kg were tolerated during LEV titration to treat seizures that were prolonged or recurrent (duration of over 5 min or over 2 episodes in 15 min) and called for acute intervention. This additional PB administration admittedly constitutes a methodological shortcoming due to the prolonged anticonvulsive efficacy of PB.

LEV was switched to oral solution as soon as the infants' condition allowed. In most cases, this coincided with the initiation of oral feeding after an initial period of full parenteral nutrition.

Neuropediatric follow-up included daily visits in the first week, weekly visits up to one month after treatment initiation, and follow-up visits at 3, 6 and 12 months. Patients were clinically examined, and seizure frequency, antiepileptic medication, and adverse events were documented at every visit. Conventional EEG was performed a week after treatment initiation, at the end of the first month, at 3, 6 and 12 months. After the first four weeks, decisions regarding further treatment were considered on an individual basis, especially regarding the duration of LEV treatment. Cerebral ultrasound was performed in all infants in the first 48 h, followed by at least two further ultrasound screenings in the first two weeks of life and weekly controls up to 40 weeks post-conceptional age. Laboratory tests including complete blood count, hepatic and renal function parameters and LEV serum levels were performed weekly during the first four weeks and at all further visits. Additional examinations were performed during rapid LEV titration in the first week and later, in the case of seizure recurrence. Based on the experience gained in older children, LEV serum levels were not used to decide LEV dosage adaptation.

Infants with occasional seizures which presented beyond the neonatal period (44 completed weeks post-conceptional age), persisted beyond the third month corrected age and correlated with the presence of epileptic spikes/sharps waves in routine EEG were considered to have developed post-neonatal epilepsy. Also infants for whom it was not indicated to taper the antiepileptic therapy because of recurrent seizures were considered to suffer from post-neonatal epilepsy. On the other hand, the classification of patients as seizure free was based on clinical observation (lack of suspicious clinical events) and conventional EEG recordings. In case of doubt a long-term conventional EEG recording or aEEG registration were further implemented. A formal statistical evaluation was not performed due to the small number of subjects included.

3. Results

In the period between 2006 and 2008, following availability of intravenous LEV, a total of 38 newborns with EEG-confirmed seizures, including 19 extremely premature infants at gestational age $<28 + 0$ weeks, birth weight 410–1330 g, 6 premature infants with gestational age >28 to $36 + 6$ weeks, birth weight 1250–1890 g, and 13 term newborns were evaluated in this study. Clinical data of all infants included in the study are summarized in Table 1, while response to treatment is presented in Table 2.

Seven newborns were affected by status epilepticus, with a frequency equally distributed between groups of different gestational age. All other newborns presented repetitive seizures, while isolated seizures prompted close surveillance, but no pharmacotherapy. In 11 out of 19 cases where seizure patterns were recognized in EEG newborns were treated with levetiracetam in the context of an acute intervention. 11 newborns required an additional application of PB 20 mg i.v. as an acute measure in the first 8 h after the diagnosis of newborn seizures and after initiation of LEV treatment, due to seizure recurrence during LEV titration. In further 8 patients a single dosage of PB 20 mg i.v. was applied in the second day after treatment initiation, while only 3 newborns received the maximal allowed PB dosage of 40 mg additional to LEV (Table 2). No other AEDs e.g. benzodiazepines were administered concurrently. Out of the 5 term infants with hypoxic-ischemic insult, three additionally underwent therapeutic hypothermia.

30 infants were seizure free under LEV at the end of the week, and 27 remained seizure free at four weeks, while EEGs markedly improved in 25 patients at four weeks. Three infants presented with seizure recurrence after the first week, in one case this led to a change in AED and initiation of a conventional PB therapy (Table 2). There was no significant difference between infants that received adjunctive PB and those that were treated with LEV alone in regards to clinical characteristics or response to treatment, although a formal statistic is

Table 1 – Clinical characteristics of patients treated with levetiracetam.

	<28 + 0 wks N (%)				28 + 0 to 36 + 6 wks N (%)				≥37 + 0 wks N (%)			
Number of patients	19				6				13			
Caesarean section	15 (79%)				4 (67%)				4 (30%)			
Gender (F/M)	F 7 (37%) M 12 (63%)				F 2 (33%) M 4 (66%)				F 5 (38%) M 8 (62%)			
Gestational age (weeks)	range: 23 + 5 to 28 + 0, median: 26				range: 29 + 6 to 35 + 4, median: 31				range: 37 + 5 to 42, median: 41			
Birth weight (g)	range: 410–1330 g, median: 842 g				range: 1250–1890 g, median: 1442 g				range: 3340–4250 g, median: 3495 g			
Apgar Score	>7	6–7	3–5	0–2	>7	6–7	3–5	0–2	>7	6–7	3–5	0–2
Apgar 1 min	3 (16%)	2 (10%)	8 (42%)	6 (32%)	–	3(50%)	–	3(50%)	3 (23%)	2 (15%)	4 (31%)	4 (31%)
Apgar 5 min	8 (42%)	7 (37%)	4 (21%)	–	2 (33%)	1 (17%)	2 (33%)	1 (17%)	7 (54%)	2 (15%)	4 (31%)	–
Apgar 10 min	17 (90%)	2 (10%)	–	–	4 (66%)	2 (33%)	–	–	9 (69%)	4 (31%)	–	–
Etiology												
Hypoxic-ischaemic insult	1 (5%)				3 (50%)				5 (38%)			
Cerebral hemorrhaege IVH/PH	9 (47%)				2 (33%)				5 (38%)			
Sepsis	12 (63%)				1 (17%)				2 (15%)			
cerebral malformation	–				–				2 (15%)			
Age at seizure onset												
<48 h	–				3 (50%)				8 (62%)			
>48 h	19 (100%)				3 (50%)				5 (38%)			
Semiology												
Subtle	12 (63%)				2 (33%)				2 (15%)			
Focal clonic	1 (5%)				–				5 (38%)			
Multifocal clonic	5 (26%)				4 (67%)				1 (8%)			
Focal tonic	2 (10%)				–				3 (23%)			
Generalized tonic	7 (37%)				2 (33%)				2 (15%)			
Myoclonic	4 (21%)				–				2 (15%)			
Neurological Status [a]												
1: Normal	8 (42%)				–				–			
2: Mildly abnormal	4 (21%)				1 (17%)				2 (15%)			
3: Moderately abnormal	5 (26%)				4 (67%)				9 (69%)			
4: Severely abnormal	2 (11%)				1 (17%)				2 (15%)			
EEG background activity[b]												
1: Normal/mild abnormalities	7 (37%)				–				1 (8%)			
2: Moderate abnormalities	6 (32%)				1 (17%)				3 (23%)			
3: Major abnormalities	6 (32%)				4 (67%)				5 (38%)			
4: Inactive EEG	–				1 (17%)				4 (30%)			
Cerebral ultrasound[c]												
1: Normal	9 (47%)				–				1 (8%)			
2: Moderately abnormal	3 (18%)				2 (33%)				4 (30%)			
3: Severely abnormal	7 (37%)				4 (66%)				8 (62%)			

a Normal: normal muscle tone, active muscle movements, normal alertness for age; Mildly abnormal: hypertonia, hyperexcitability; Moderately abnormal: hypotonia/hypertonia, decreased muscle movements, lethargy; Severely abnormal: flaccid, inactive and coma.
b EEG-scoring according to Holmes and Lombroso.
c Normal: no pathology; Moderately abnormal: IVH I/II, mild ventriculomegaly, periventricular echodensities; Severely abnormal: IVH III/IV, cystic PVL, malformation.

impracticable due to the size of the study population. The limited number of newborns included further prohibits any definite conclusions as to the response to LEV in newborn seizures of different etiology. However, there was a trend for poor response among patients with extensive intracerebral hemorrhage.

In 19/30 cases, LEV was discontinued after 2–4 weeks seizure freedom. In view of multiple comorbidities especially associated with extreme prematurity, LEV was continued in 7 cases up to 3 months after treatment initiation. Drowsiness was the only adverse effect observed in infants during the titration period, often concomitant with adjunctive PB therapy.

LEV plasma levels were in the range of 12,5–55 μg/ml (reference values 5–65,0 μg/ml) under intravenous administration and remained in the same therapeutic range when switching from intravenous to oral. There was no significant variation in LEV plasma levels between newborns that received 1–2 additional doses of PB compared to those where this intervention was not necessary.

Follow-up data is available on patients that remained seizure-free under LEV at 4 weeks after treatment initiation . At 6 months 4/14 premature infants developed post-neonatal epilepsy, 7/14 presented developmental delay and 5/14 multiple comorbidities. In the newborn group, 2/12 developed epilepsy and 5/12 were diagnosed with developmental delay, while 1/12 had comorbidities. At 12 months 3/14 extremely premature infants had post-neonatal epilepsy and 5/14 presented with developmental delay compared to 2/12 with post-neonatal epilepsy and 3/12 with developmental delay in the newborn group (Table 3).

Table 2 – Anticonvulsant efficacy of levetiracetam.

	<28 + 0 wks N (%)		28 + 0 to 36 + 6 wks N (%)		≥37 + 0 wks N (%)	
Number of patients initially included in the study	19		6		13	
PB administration in the first 2 d of titration	8 (42%)		4 (67%)		7 (54%)	
PB administration > 3 d = excluded from further study	5 (26%)		2 (33%)		1 (8%)	
Number of patients in the study at 3 d	14		4		12	
	adj. PB	no PB	adj. PB	no PB	adj. PB	no PB
Seizure free under LEV at 7 d	3 (21%)	11 (79%)	1 (25%)	3 (75%)	6 (50%)	6 (50%)
Seizure recurrence after 7 d	1 (7%)	–	1 (25%)	–	–	–
Seizure free at 30 d	1 (5%)	10 (71%)	1 (25%)	3 (75%)	6 (50%)	6 (50%)
Single seizure recurrence, no change in treatment	–	1 (5%)	1 (25%)	–	–	–
Change of AED or combination therapy	1 (5%)	–	–	–	–	–
EEG pattern normalization						
1wk	2 (14%)	10 (71%)	–	1 (25%)	1 (8%)	4 (33%)
1mo	3 (21%)	11 (79%)	1 (25%)	2 (50%)	3 (25%)	4 (33%)
Treatment duration						
2–4 wks	9 (47%)		4 (67%)		6 (46%)	
5–8 wks	1 (5%)		–		2 (15%)	
9–12 wks	3 (18%)		–		4 (30%)	

adj. PB: adjunctive phenobarbital.

Infants with post-neonatal epilepsy commonly presented symptomatic localization-related epilepsy with focal motor seizures and secondary generalization regardless of gestational age. None of them presented electro-clinical patterns consistent with West syndrome. However, there was a strong correlation of post-neonatal epilepsy with developmental delay ranging from mild retardation to cerebral palsy.

4. Discussion

The causes of neonatal seizures vary as do the duration and frequency, and the distinction between an epileptic and non-epileptic event in neonates is often difficult to demonstrate.[25] On the other hand, current data from animal and human studies suggest that neonatal seizures affect the developing brain with long-term adverse effects on cognition, learning, and seizure threshold,[26,27] and when a suspicious event is confirmed electrographically, treatment seems warranted. Repeated seizures may be deleterious to the brain even without disturbances of ventilation or perfusion by increasing central nervous system metabolic demand and causing the release of excitatory amino acids such as glutamate.[28]

Table 3 – Outcome at 6 and 12 months after treatment initiation.

Outcome	<28 + 0 wks N (%)	28 + 0 −36 + 6 wks N (%)	≤37 + 0 wks N (%)
Number of patients	11	3	12
Mortality	–	1 (17%)	–
6 mon			
Post-neonatal epilepsy	3 (27%)	1 (33%)	2 (17%)
Developmental delay	6 (55%)	1 (33%)	5 (42%)
Co-morbidity	5 (45%)	–	1 (8%)
12 mon			
Post-neonatal epilepsy	3 (27%)	–	2 (17%)
Developmental delay	5 (45%)	–	3 (25%)
Co-morbidity	4 (36%)	–	–

Infants in which occasional seizures continued after the neonatal period, considered up to 44 completed weeks' post-conceptional age for preterm infants born <37 weeks of GA, and persisted beyond the third month of corrected age with the presence of epileptic spikes/sharps waves in their routine EEG or infants for whom it was impracticable to taper the antiepileptic therapy because of recurrent seizures were considered as suffering from post-neonatal epilepsy.

The most common anticonvulsant used initially in the newborn period for seizure treatment is intravenous PB[29] although there are many concerns regarding the short-term adverse effects of PB as well as long-term effect on neurocognitive development. Intravenous phenytoin and benzodiazepines are commonly employed as second-line intravenous medications in the treatment of neonatal seizures.[30] The adverse effects of phenytoin are well known and include cardiac arrhythmias and hypotension. Fosphenytoin may be a safer alternative but is less well studied and is not available in every country. Benzodiazepines have been successfully used to stop status epilepticus, but the long-term use of these medications is not recommended. Midazolam,[31] carbamazepine, primidone, lidocaine, and valproate[6,32] are other medications that have been used with limited data on success and safety.[29]

The potentially neurotoxic effects of antiepileptic drugs have been known for decades. Intrauterine exposure to phenobarbital and phenytoin is a risk factor for birth defects, microcephaly, mental retardation, and learning deficits or lower IQ scores that persist to adulthood.[33–36] Furthermore, infants and toddlers randomized to prophylactic phenobarbital therapy for febrile seizures had lower IQ scores that outlasted the duration of treatment.[37,38] A more recent study showed that clinically relevant levels of antiepileptic drugs including phenobarbital, phenytoin, and diazepam led to apoptotic neurodegeneration in the developing rat brain.[8] The impact of therapeutic doses of these agents on neurodevelopmental outcome in newborns with seizures is not known.

LEV, a novel anticonvulsant drug with a nonconventional mechanism of action, is well studied as an adjunctive therapy for partial epilepsy. Given the safety profile of this medication

as well as its linear pharmacokinetics (half-life of 7 h),[39] rapid absorption (30 min), nonhepatic elimination, lack of protein binding (<10%), no known interactions with other antiepileptic drugs, and favorable efficacy in children,[12,40] it is empirically considered a viable alternative for seizure treatment in all pediatric age groups, including infants and neonates.[41]

Several pediatric studies have reported marked decrease in seizure frequency with the use of LEV, including a recent report of six patients that received LEV as a first-line AED, allowing 1–2 additional doses of PB during titration.[23] Furthermore, in a recent survey conducted at the 2007 Annual Meeting of the Child Neurology Society, seventy-three percent (40/55) of pediatric neurologists present recommended treatment of neonatal seizures with one or both of LEV and topiramate (TPM); 47% (26/55) recommended LEV; and 55% (30/55) recommended TPM.[42] Factors driving LEV use in the intensive care nursery may include a low side-effect profile and its ease of use with either parenteral or liquid formulations.

In our study, we observed the anticonvulsant efficacy and safety of LEV as a first-line AED in neonatal seizures, after excluding standard metabolic causes. 30/38 (79%) infants were seizure free under LEV at the end of the first week, and 27/30 (90%) remained seizure free at four weeks, while EEGs were markedly improved in 25/30 (83%) patients at four weeks. Three infants presented with seizure recurrence after the first week; in one case this led to a change in AED. LEV was tolerated extremely well in our study group, with somnolence during titration (at least partially) attributed to adjunctive PB therapy. Plasma levels of LEV were in the therapeutic range in all occasions, including when changing administration from intravenous to oral. This observation underlines the safety of LEV administration in an ICU setting and suggests a high practicability of use.

Our study has various limitations: 1. it was a non-randomized study with a relatively small sample size and no control group; 2. adjunctive PB therapy in some patients was tolerated during LEV titration, thus constituting a methodological shortcoming due to the prolonged anticonvulsive efficacy of PB; 3. simultaneous video-EEG monitoring was not performed. Certain abnormal clinical behavior, even without EEG epileptiform manifestation, may represent subcortical seizures. Seizure control under LEV monotherapy cannot be clearly attributed to LEV alone in all cases, since this treatment was in some cases inadequate to control seizures leading to an adjunctive PB therapy. On the other hand, most newborns that received LEV alone remained seizure free and there was no major discrepancy in efficacy measures in comparison with infants that received additional PB. It is important to remember that most symptomatic seizures due to hypoxic-ischemic encephalopathy (the most common cause of seizures in the newborn) often wane abruptly by the end of the first week of life, although AED therapy is commonly continued by most physicians.[5,32]

We treated newborns with EEG-confirmed seizures, thus avoiding the common practice of responding to suspicious newborn movements alone, which may lead to treating some babies with non-epileptic movements with potentially harmful anticonvulsants.[43] On the other hand, electroencephalographic seizures with no clear-cut clinical manifestations ("electroclinical dissociation") are a common occurrence in neonates with abnormal neurological findings.[44,45] We did not attempt a further increase of LEV dosage, in accordance with usual dosage of LEV in children and adults ranging from 30 to 60 mg/kg/d. However, clearance of LEV is significantly higher in infants[46] and doses over 100 mg/kg/d without side effects have been reported in very young children.[21,13] It is not clear, whether our patients may have had additional benefit from further increase in LEV dose.

LEV was discontinued at 2–4 weeks in 19 cases, but continued for 9–12 weeks in 7 cases, due to multimorbidity. Although neonatal seizures are an important risk factor for childhood epilepsy, the timing of onset of post-neonatal seizures is variable and seizures may recur in spite of prophylactic antiepileptic drug therapy, making the value of ongoing therapy uncertain.[47,3] Most experts recommend early cessation of antiepileptic drug therapy due to the high side-effect profile of old AEDs coupled with the fact that neonatal seizures typically abate within days independent of the therapeutic intervention and have a low risk of early recurrence.[48]

In follow-up, favorable response to treatment with cessation of seizures and EEG normalization was associated with a favorable neurodevelopmental outcome, as reported in term neonates.[4] At 12 months 3/14 extremely premature infants developed post-neonatal epilepsy and 5/14 presented with developmental delay compared to 2/12 with post-neonatal epilepsy and 3/12 with developmental delay in the newborn group. In our patient group, we observed an association of outcome with etiology, as suggested by previous studies,[49] although the limited number of patients treated did not allow for statistical analysis.

The encouraging results obtained in this population illustrate the safety of LEV treatment in neonatal seizures, including prematurity, and suggest LEV anticonvulsant efficacy. Double blind prospective controlled studies and long-term evaluation of cognitive outcome is called for, in order to establish a reasonable alternative to PB.

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