6. Schwabova J, Brozkova DS, Petrak B, Mojzisova M, Pavlickova K, Haberlova J, et al. Homozygous *EXOSC3* mutation c.92G→C, p.G31A is a founder mutation causing severe pontocerebellar hypoplasia type 1 among the Czech Romani. J Neurogenet. 2013;27:163–9.

Anna Paola Di Giovambattista*, Itxaropena Jácome Querejeta, Purificación Ventura Faci, Gerardo Rodríguez Martínez, Feliciano Ramos Fuentes

Servicio de Pediatría, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain

* Corresponding author.
E-mail address: annadigiov@live.it (A.P. Di Giovambattista).

2341-2879/

Use of levetiracetam in neonatal seizures☆

Uso de levetiracetam en crisis convulsivas neonatales

Dear Editor:

Neonatal seizures (NSs) occur in 1.5 per 1000 live births, with a higher incidence in preterm newborns. They usually result from asphyxia, haemorrhage, brain malformations, metabolic disturbances, inborn errors of metabolism or infection.[1] The challenges posed by its diagnosis and the decision of which children to treat are compounded by the growing evidence on the deleterious effects of the drugs approved for this purpose: phenobarbital and phenytoin. Both achieve seizure reduction in at least 50% of cases, and have been associated with neuronal apoptosis in animal models. For this reason, other drugs that have fewer apparent side effects are increasingly being used off-label. Levetiracetam (LEV) was approved by the Food and Drug Administration in 2012[2] for the treatment of partial-onset seizures in children aged 1 month and older.

We reviewed the use of LEV in newborns admitted to our unit between January 2011 and May 2016. Table 1 summarises the characteristics of these patients. Twenty-three newborns were treated. Their weights ranged between 1610 and 4100 g, and 17.4% had been born preterm. Table 2 presents data on the types of seizures, diagnostic tests and outcomes.

Levetiracetam was used as the first-line agent in 17.4% of the patients, and was the second-line agent in 73.9%, in most cases after phenobarbital failure. In 15 patients (65.2%), treatment was initiated with an intravenous loading bolus at a dose of 10–50 mg/kg. A maintenance dose was used in 91.3% that ranged between 10 and 40 mg/kg/2 doses, with increases of 10 mg/kg every three to five days. Out of the 19 patients in which it was used as the second-line agent, the dose of the first-line agent could be reduced in 63.1% in the first week after initiation of LEV. In eight patients, there was no improvement in either clinical or electrical seizures in the first 24 h, but 15 patients (65.2%) did improve (with improvement understood as the cessation of seizures or a reduction in frequency of at least 50%). We did not find evidence of adverse effects in any of the patients. There was treatment limitation in four patients, which was unrelated to the use of LEV. Of the 19 remaining patients, 88.9% were discharged with a LEV regimen (77.8% as monotherapy).

The use of LEV in NSs is becoming increasingly frequent despite not having been approved, as it is the case of most anticonvulsant agents used in infants. It is more recommended by paediatric neurologists than by neonatologists.[1,2] A retrospective chart analysis[3] identified 72 newborns treated with LEV, most of them born preterm, and found no adverse effects leading to treatment discontinuation. The definition of seizure was based on clinical features only, as aEEG or EEG were not used, so the efficacy results of this study are debatable. Previous studies have included between six and thirty-eight newborns,[2] and some were exclusively on preterm neonates ($n = 12$).[4] One prospective study[5] in 38 newborns in which LEV was used as the first-line agent found clinical improvement, and the EEG taken at one week post birth in 30 of these newborns showed no evidence of side effects, although the protocol tolerated the administration of two doses of phenobarbital during LEV titration, so that phenobarbital or the natural course of the seizures may have influenced the results. There is a published case of anaphylaxis following infusion of LEV in a neonate,[6] and it is possible that children with complex clinical situations and previous management are difficult to identify. A recent study found an association between LEV and neuronal cell death in newborns with asphyxia not treated with hypothermia.[6] Given the scarcity of the evidence on newborns, the safety of this drug for the first-line treatment of NSs remains to be determined, and most current guidelines that include LEV do so as a second-line agent.

There are limitations to this review. In addition to its retrospective design, the number of cases is small, although we have not found any other Spanish publication on the subject; our unit was not equipped with video-EEG to diagnose seizures, although we used aEEG and EEG to guide the treatment. A larger sample size would help determine whether there is an association between gestational age or the aetiology of the seizures and the response to LEV.

In conclusion, LEV is increasingly being used for the treatment of NSs, usually as the second-line agent. It seems to be at least as effective as classical anticonvulsants. Since it was associated with few side effects and seems to be less harmful to the brain, LEV is a drug to consider, even in preterm newborns. Prospective studies are needed to learn the effects of this drug in the short and long term.

☆ Please cite this article as: Lloreda-García JM, Fernández-Fructuoso JR, Gómez-Santos E, García-González A, Leante-Castellanos JL. Uso de levetiracetam en crisis convulsivas neonatales. An Pediatr (Barc). 2017;86:286–288.

Table 1 Patient characteristics.

Case	Gestational age/sex	Birth weight (g)	Apgar 1–5 min	Days of life at admission	Aetiology	Order of use	Indication	Initial route	Loading dose	Maximum maintenance dose in hospital	Days of LEV during stay	Favourable response at 24 h	Length of stay	Treatment at discharge	Adverse effects
1	41/F	3000	9–10	2	Brain haemorrhage	2	Refractory to PB	IV	40 mg/kg	No	2	No	1	PB	No
2	39/M	3337	4–6	7	Asphyxia	1	Seizures	Oral		30 mg/kg in 2 oral doses	3	Yes	6	LEV	No
3	38/F	2420	9–10	25	Brain malformation	1	Seizures	IV	10 mg/kg	35 mg/kg in 2 oral doses	3	Yes	66	LEV, PB	No
4	38/M	3200	1–4	1	Asphyxia	2	Refractory to PB	IV	30 mg/kg	No	1	No	1	No	No
5	35/F	2154	0–0	1	Asphyxia	2	Refractory to PB	IV	20 mg/kg	10 mg/kg IV	1	No	2	Death	No
6	40/M	3100	9–10	15	Out-of-hospital asphyxia	2	Refractory to PB	IV	10 mg/kg	20 mg/kg in 2 oral doses	1	Yes	6	LEV	No
7	39/M	3591	5–8	1	Asphyxia	2	Refractory to PB	IV	20 mg/kg	40 mg/kg/day in 2 oral doses	2	No	8	LEV	No
8	39/M	4100	9–10	1	Brain malformation	2	Switch to LEV	Oral		60 mg/kg/day in 2 doses	2	Yes	23	LEV, VAL	No
9	34/F	2415	0–4	1	Asphyxia	2	Refractory to PB	IV	50 mg/kg	40 mg/kg/day in 2 doses	1	No	45	LEV	No
10	38/F	2935	1–3	1	Asphyxia	3	Refractory to PB	IV	10 mg/kg	10 mg/kg IV	3	Yes	5	Death	No
11	40/M	3650	7–9	2	Idiopathic	2	Refractory to PB	IV	40 mg/kg	60 mg/kg/day in 2 doses	5	No	40	LEV	No
12	40/F	3400	3–7	1	Asphyxia	2	Refractory to PB	IV	20 mg/kg	40 mg/kg/day in 2 doses	1	Yes	11	LEV	No
13	34/F	2230	7–8	1	Idiopathic	1	Seizures	Oral		20 mg/kg/day in 2 doses oral	3	Yes	5	LEV	No
14	39/F	3200	9–10	3	Cerebral infarction	1	Seizures	Oral		10 mg/kg oral in 2 doses	7	Yes	5	LEV	No
15	37/F	1610	6–9	1	Syndromic	2	Switch to LEV	Oral		30 mg/kg in 2 oral doses	6	Yes	29	LEV	No
16	39/M	2500	9–10	8	Brain malformation	2	Switch to LEV	Oral		30 mg/kg in 2 oral doses	3	Yes	25	LEV	No
17	41/F	3900	9–10	9	Brain haemorrhage	2	Refractory to PB	IV	10 mg/kg	10 mg/kg IV	1	Yes	2	Death	No
18	37/F	2120	9–9	1	Hypoglycaemia	2	Refractory to PB	IV	10 mg/kg	35 mg/kg in 2 oral doses	2	No	11	LEV	No
19	37/M	3000	9–10	20	Pneumococcal meningitis	2	Refractory to PB	IV	15 mg/kg	20 mg/kg IV	1	No	10	Death	No
20	41/M	3890	9–10	3	Brain malformation	2	Refractory to PB	IV	10 mg/kg	10 mg/kg oral in one dose	4	Yes	7	LEV	No
21	39/M	3200	9–10	4	Idiopathic	2	Refractory to PB	IV	20 mg/kg	30 mg/kg in 2 oral doses	2	Yes	10	PHEN, OXC	No
22	41/M	3490	9–10	1	Idiopathic	5	Switch to LEV	Oral		25 mg/kg in 2 doses	15	Yes	5	LEV	No
23	35/M	3680	3–6	1	Asphyxia	2	Switch to LEV	Oral		30 mg/kg in 2 oral doses	6	Yes	13	LEV	No

F, female; LEV, levetiracetam; M, male; PB, phenobarbital; PHEN, phenytoin; OXC, oxcarbazepine; VAL, valproic acid.

Table 2 Seizure characteristics and diagnostic tests.

	N (%)
Type of seizures	
Clonic	21 (91.2)
Subtle only	1 (4.4)
Tonic	1 (4.4)
Causes	
Asphyxia	9 (39.1)
Brain malformation	5 (21.7)
Haemorrhage	3 (13)
Idiopathic	3 (13)
Infection	1 (4.4)
Metabolic	1 (4.4)
Hypoglycaemia	1 (4.4)
Diffusion-weighted MRI	21 (91.2)
Abnormal MRI	15 (71.4)
Head ultrasound only	2 (8.8)
Abnormal	2 (100)
*aEEG**	21 (91.2)
Seizures	17 (81)
Abnormal background pattern only	4 (19)
EEG	22 (95.6)
Abnormal	14 (63.6)

EEG, electroencephalogram; MRI, magnetic resonance imaging.
*aEEG**: amplitude-integrated electroencephalogram.

This review had the approval of the hospital's ethics committee.

References

1. Hellström-Westas L, Boylan G, Ågren J. Systematic review of neonatal seizure management strategies provides guidance on anti-epileptic treatment. Acta Paediatr. 2015;104:123–9.
2. Mruk AL, Garlitz KL, Leung NR. Levetiracetam in neonatal seizures: a review. J Pediatr Pharmacol Ther. 2015;20:76–89.
3. Neininger MP, Ullmann M, Dahse AJ, Syrbe S, Bernhard MK, Frontini R, et al. Use of levetiracetam in neonates in clinical practice: a retrospective study at a German university hospital. Neuropediatrics. 2015;46:329–34.
4. Khan O, Cipriani C, Wright C, Crisp E, Kirmani B. Role of intravenous levetiracetam for acute seizure management in preterm neonates. Pediatr Neurol. 2013;49:340–3.
5. Koklu E, Ariguloglu EA, Koklu S. Levetiracetam-induced anaphylaxis in a neonate. Pediatr Neurol. 2014;50:192–4.
6. Griesmaier E, Stock K, Medek K, Stanika RI, Obermair GJ, Posod A, et al. Levetiracetam increases neonatal hypoxic-ischemic brain injury under normothermic, but not hypothermic conditions. Brain Res. 2014;1556:10–8.

Jose Maria Lloreda-García*, Jose Ramón Fernández-Fructuoso, Elisabeth Gómez-Santos, Ana García-González, Jose Luis Leante-Castellanos

Unidad de Neonatología y UCI Neonatal, Hospital Universitario Santa Lucía, Complejo Hospitalario Universitario de Cartagena, Cartagena, Murcia, Spain

* Corresponding author.
E-mail address: jmlloreda@gmail.com
(J.M. Lloreda-García).

2341-2879/