■ Clinical commentary

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Efficacy of lacosamide in neonatal-onset super-refractory status epilepticus: a case report

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ABSTRACT – We report the case of a previously healthy newborn who developed super-refractory status epilepticus after Group B streptococcal meningoencephalitis. After administration of first-, second- and third-line anticonvulsants without resolution of status epilepticus, we started intravenous lacosamide as adjunctive therapy to phenobarbital, phenytoin and continuous infusion of ketamine and midazolam. After administration of lacosamide, we observed a clear-cut improvement in the neurological clinical condition coupled with seizure control on continuous video-EEG monitoring, even after suspension of all other medications except for phenobarbital. No adverse effects ascribable to lacosamide were reported. The available data regarding the use of lacosamide for status epilepticus in adults and children are promising, although there is as yet only anecdotal evidence for neonatal status epilepticus. Its lack of potential interactions, good tolerability and the option of intravenous use lend to its appeal as treatment for status epilepticus. To the best of our knowledge, this is one of the first reported cases of effective lacosamide infusion in neonatal-onset super-refractory status epilepticus. This evidence should prompt further investigation on efficacy and safety of lacosamide to support its use in this population.

Key words: neonatal; newborn; lacosamide; status epilepticus; super refractory status epilepticus

According to the third London-Innsbruck Colloquium on Status Epilepticus in 2011, super-refractory status epilepticus (SRSE) is defined as a status epilepticus that continues or recurs 24 hours or more after the onset of anaesthetic therapy, including those cases in which status epilepticus recurs upon reduction or withdrawal of anesthesia [1].

It represents a major diagnostic and therapeutic challenge and is an uncommon condition in the newborn, associated with high mortality rates and poor neurodevelopmental outcomes among survivors [2].

There is shortage of high-level evidence-based data to guide treatment of neonatal seizures and status epilepticus. Phenobarbital and phenytoin are still considered first and second-line treatment in practice, respectively [3]. Nevertheless, there is increasing evidence of phenobarbital neurotoxicity and long-term sequelae in neonatal mammalian models [4,5]. Studies on benzodiazepine efficacy in neonatal seizures is limited and conflicting. Several other pharmacological options showed suboptimal data on efficacy and safety regarding their use in this population [3], but further exploration of newer anticonvulsant agents such as levetiracetam and topiramate is of particular interest, due to the lack of neuronal apoptosis in animal models [6,7].

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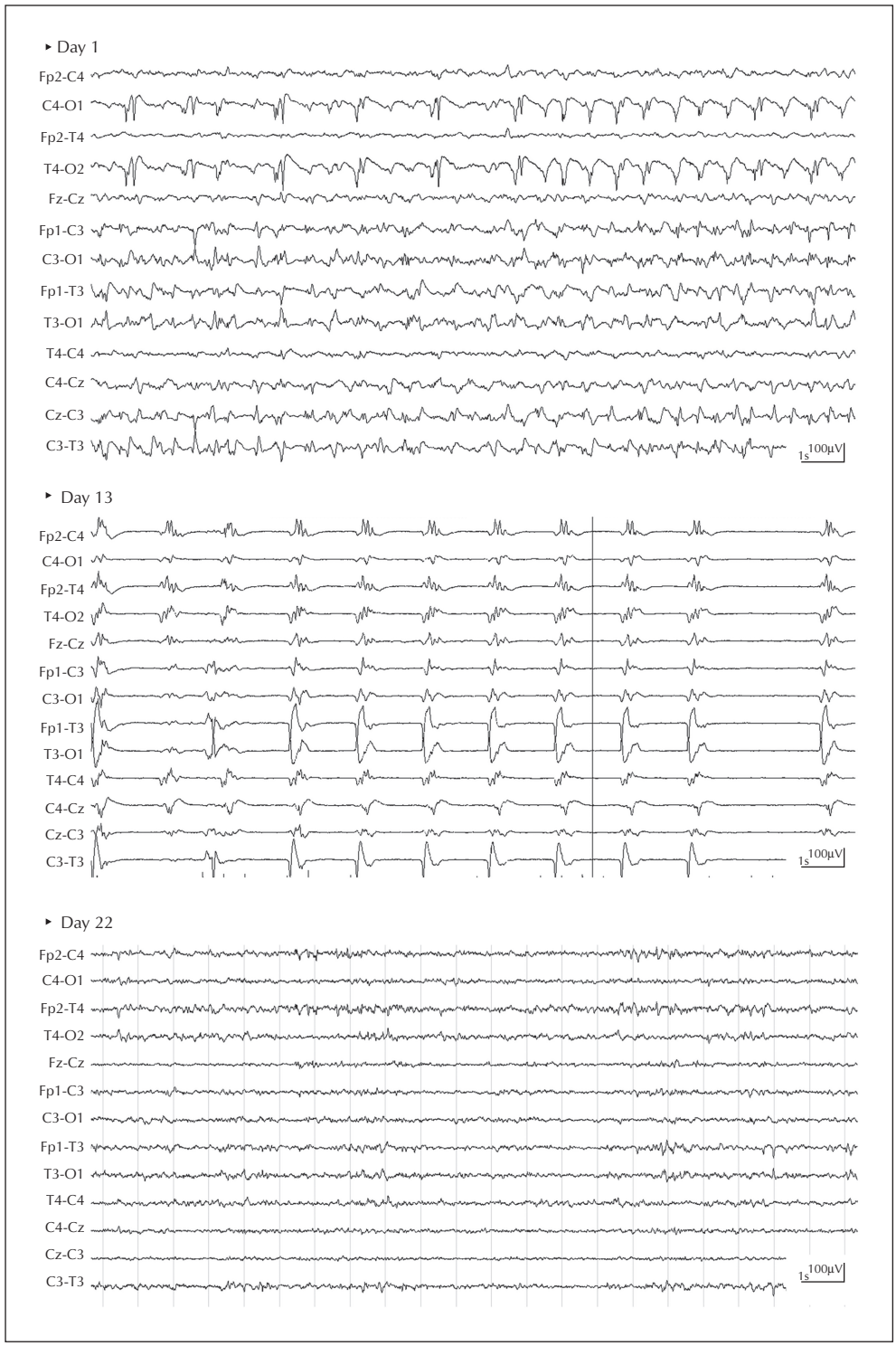
Lacosamide is one of the newest medications and functions through selectively enhancing slow inactivation of voltage-gated sodium channels, without affecting fast inactivation, decreasing pathological neuronal hyperexcitability without a reduction in normal neuronal physiological function. Lacosamide is also hypothesized to produce a neuroprotective effect, preventing the formation of abnormal neuronal connections [8].
Currently, in Italy, lacosamide is registered as monotherapy or adjunctive therapy for the treatment of focal-onset seizures with or without secondary generalization in adults, adolescents and children, four years of age and older, affected by epilepsy.
Lacosamide is established as a treatment for status epilepticus in adults and children [8,9] and its lack of potential interactions along with the option of intravenous use lend to its appeal. There is so far only anecdotal evidence for the use of lacosamide as treatment for neonatal status epilepticus and there is currently insufficient data for its safe use in the neonatal period.
We describe a case report of symptomatic super-refractory status epilepticus in a newborn caused by Group B streptococcal (GBS) meningoencephalitis at the tertiary care referral hospital of Padua, Italy. Moreover, we conducted a literature review, in PubMed (up to October 2020), of English and Italian articles with the following search key words "(lacosamide) and (status epilepticus) and (neonatal or neonate or newborn or child or children or infant or infants or paediatric)".

Case study

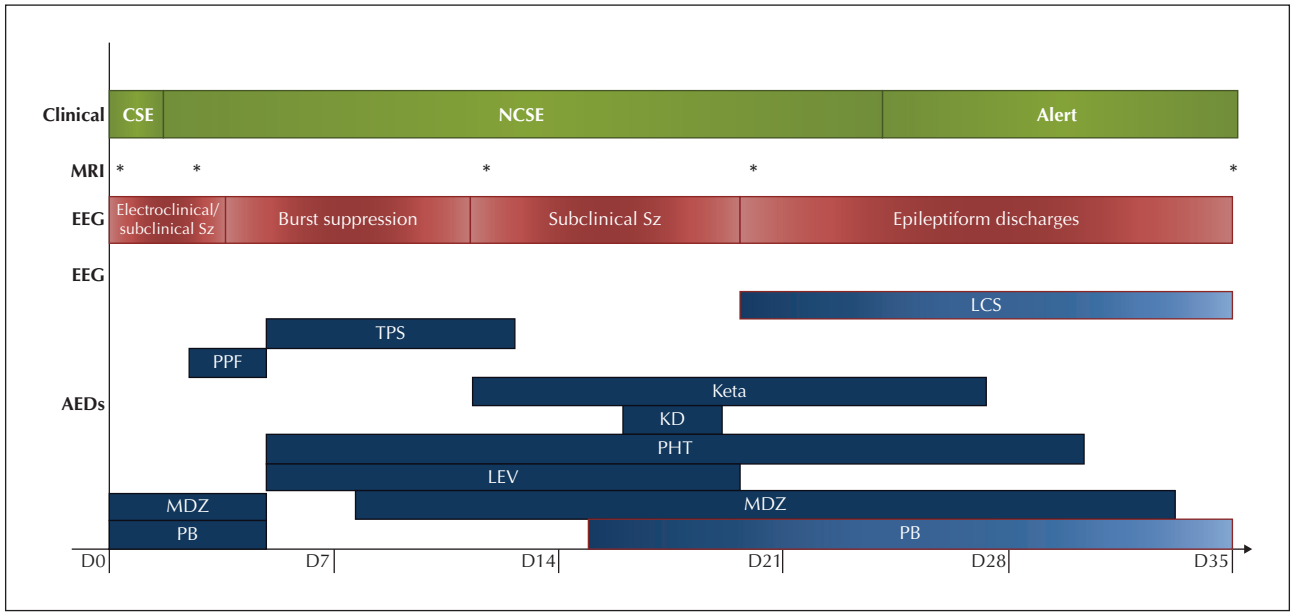
A previously healthy 15-day-old male newborn was admitted to our tertiary care hospital with fever and elevated serum levels of C-reactive protein and procalcitonin, therefore broad-spectrum antibiotic therapy was promptly started. In the next few hours, the patient quickly developed irritability and focal motor seizures evolving to bilateral tonic-clonic seizures, unresponsive to first-line treatment with phenobarbital. Cranial ultrasound showed a hyperechogenic area in the left frontal lobe (15 x 22 mm).
As the patient's condition worsened, he was sedated and intubated. Clinical signs and symptoms, neuroimaging findings and the identification of *Streptococcus agalactiae* in blood and cerebrospinal fluid conveyed a diagnosis of sepsis and meningoencephalitis with development of cerebral vasculitis and ischemic-haemorrhagic lesions extensively throughout the cerebral cortex (especially left frontal cortex and subcortex), nucleo-capsular regions and hypothalamus with subsequent necrotic-atrophic evolution (*supplementary figure 1*). The patient also developed extensive cerebral venous sinus thrombosis and arterial thrombosis, treated with unfractioned heparin.
We tried to achieve seizure control with different intravenous antiepileptic drugs: phenobarbital at 3.5 mg/kg q12h (maximum trough level: 193 µmol/L; reference value: 43-173 µmol/L); phenytoin at 6 mg/kg q12h (trough level: 104 µmol/L; reference value: 40-79 µmol/L); and levetiracetam at 33 mg/kg q12h (maximum trough level: 50 mg/L; reference value: 10-40 mg/L). Continuous infusion of sedatives (maximum dosage for each drug: midazolam at 1 mg/kg/h, propofol at 3 mg/kg/h, sodium thiopental at 5 mg/kg/h, and ketamine at 100 mcg/kg/min) was also carried out.
A brief trial with the ketogenic diet was quickly suspended due to intolerance. Unfortunately, the patient persisted with super-refractory status epilepticus, confirmed by continuous video-EEG recording (*figure 1*).
After obtaining written parental consent, 20 days after onset of SE, we administered an intravenous bolus of lacosamide (8 mg/kg) followed by an IV maintenance dosage of 5 mg/kg q12h (maximum trough level: 1.5 mg/L; reference value: 1-10 mg/L) as adjunctive therapy to phenobarbital and phenytoin and continuous infusion of ketamine and midazolam.
Two hours after the introduction of lacosamide, we observed a clear-cut improvement in the neurological clinical condition, coupled with subclinical seizure control on continuous video-EEG monitoring, thus allowing gradual weaning and suspension of all sedatives. The patient reached full alertness four days after first administration of lacosamide.
No adverse effects ascribable to lacosamide were reported; in particular, we checked for cardiac rhythm disturbances through repeated electrocardiograms (EKGs), however, we never observed PR prolongation, arrhythmias, nor other heart rate anomalies.
Later on, it was possible to wean off the other antiepileptic drugs, except for phenobarbital, and 90 days after introduction of lacosamide, the patient is still seizure-free. Long-term EEG monitoring has not shown electroclinical seizures so far and the patient is treated with oral lacosamide and phenobarbital (*figure 2*).

Discussion

Lacosamide enhances inhibition of slow sodium channels and is used predominantly as adjunctive therapy for focal-onset seizures, but it also has an emergent promising role as treatment for status epilepticus and refractory status epilepticus due to the intravenous formulation and good tolerability in older infants [10].
In our case, we did not experience any cardiac events or anomalies on EKG. Although a small dose-related



■ **Figure 1.** EEG recording of the patient at the onset of status epilepticus on Day 1 with IV midazolam and phenobarbital (upper panel), on Day 13 during the course of the disease with IV ketamine, phenytoin, levetiracetam and midazolam (middle panel), and on Day 22 with lacosamide, IV ketamine, phenytoin, midazolam and phenobarbital (lower panel).



■ **Figure 2.** Timeline of the clinical course of the patient.

prolongation of PR interval, with no evident symptomatic consequence, has been described with the use of lacosamide in the adult population [11], studies involving either adults or children 10 have not reported major cardiac events. This good safety profile could be relevant to newborns and infants as well. In neonatal rats, lacosamide was found to exert a neuroprotective effect on hypoxia-ischemia, which suggests a potential supplementary benefit in the neonatal population under hypoxic-ischemic conditions, including heart surgery [12].

To the best of our knowledge, evidence for the use of lacosamide as treatment for neonatal-onset status epilepticus is anecdotal. We found one study in the literature, a case series by Arkilo *et al.*, reporting the use of intravenous lacosamide in a four-week-old female newborn with super-refractory status epilepticus caused by GBS meningitis (10 mg/kg initial dose; other concurrent drugs included levetiracetam, phenobarbital, and continuous infusion of pentobarbital). No adverse events were observed in the newborn, however, lacosamide proved ineffective in ceasing seizure activity [13].

Both phenytoin and lacosamide target voltage-gated sodium channels, although lacosamide affects sodium channel slow inactivation without apparently affecting fast inactivation. Even though, in our case, the temporal relationship seems to strongly favour a role of lacosamide in the resolution of SRSE, we cannot rule out the possibility that lacosamide was effective due to a synergistic effect with phenytoin, thus possibly explaining why, in the case described by Arkilo *et al.*, lacosamide alone was not successful in stopping seizure activity.

We have also taken into consideration the possibility that, in our case, seizures resolved for other unknown reasons after a long period of SRSE, although this seems less probable due to the fact that, after the introduction of lacosamide, not only seizure activity ceased but the whole EEG pattern drastically improved.

Flor-Hirsch *et al.* reported the case of a female newborn with *SCN2A*-related intractable neonatal seizures, who showed complete seizure control following lacosamide administration on the 35th day of life, in addition to a combination of other anticonvulsants [14]. In this case, the use of lacosamide was specifically chosen as target therapy since the patient had a sodium channelopathy (*SCN2A*) and because there had been temporary control of focal seizures after administration of phenytoin and oxcarbazepine.

Although these cases are isolated reports, the data may be of use for further investigation of the potential role of lacosamide in neonatal-onset SE.

Taken together, favourable pharmacokinetic characteristics, a good safety profile, ease of preparation and administration, minimal interaction with other drugs, and easy conversion to oral maintenance therapy make lacosamide a potential second-line anticonvulsant as treatment for neonatal-onset convulsive status epilepticus, as an alternative to phenytoin and/or phenobarbital or when these drugs have failed. Comparative trials would be desirable to provide evidence in favour of this use of lacosamide.

In the meantime, our unique experience suggests that lacosamide may be considered in selected cases as a potentially effective and safe drug for the treatment of neonatal-onset status epilepticus, especially before starting prolonged and demanding anaesthetic treatment. ■

Supplementary material.
Summary slides accompanying the manuscript and supplementary figure are available at www.epilepticdisorders.com.

Disclosures.
None of the authors have any conflicts of interest to disclose.

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TEST YOURSELF

(1) What is the latest definition of super-refractory status epilepticus?

A. A seizure with a duration equal to or greater than 30 minutes, or a series of seizures during which the patient does not regain normal mental status between seizures.
B. A status epilepticus that continues or recurs 24 hours or more after the onset of anaesthetic therapy, including those cases in which status epilepticus recurs upon reduction or withdrawal of anaesthesia, according to the 3rd London-Innsbruck Colloquium on Status Epilepticus in 2011.
C. A status epilepticus that has not responded to first-line therapy (benzodiazepine) or second-line therapy, and that, according to treatment protocols, requires the application of general anaesthesia.

(2) What is the known mechanism of action of lacosamide?

A. Lacosamide enhances fast inactivation of voltage-gated sodium channels.
B. Lacosamide enhances both fast and slow inactivation of voltage-gated sodium channels.
C. Lacosamide enhances slow inactivation of voltage-gated sodium channels.

(3) What is the major current indication for lacosamide use in older children and adults?

A. Lacosamide is used predominantly as adjunctive therapy for focal-onset seizures.
B. Lacosamide is used predominantly as adjunctive therapy for genetic generalized epilepsy.
C. Lacosamide is used exclusively as target therapy in sodium channelopathies.

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".