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Case report

Successful treatment of childhood prolonged refractory status epilepticus with lacosamide

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ABSTRACT

Prolonged, refractory status epilepticus is a rare clinical syndrome that is associated with severe morbidity and mortality. Lacosamide is a newly approved medication for treatment of partial onset seizures in adults, which has a novel mechanism of action. Experimental data and recent reports suggest that lacosamide could be effective in status epilepticus. We report a child with prolonged, refractory status epilepticus that persisted for 10 weeks despite treatment with multiple anti-epileptics and anesthetics and was then aborted with lacosamide. This is the first report of the effect of lacosamide in prolonged refractory status epilepticus, and the first report of lacosamide efficacy in status epilepticus in a child.

1. Introduction

Status epilepticus (SE) is a life-threatening medical emergency. It is defined as ongoing seizures or repetitive seizure activity lasting more than 30 min without recovery of consciousness between seizures. Status epilepticus that persists despite first and second-line antiepileptic therapy has been defined as refractory status epilepticus (RSE) and occurs in 10–40% of SE cases.[1] In a rare subset of patients, RSE may persist for weeks or months. If status epilepticus persists for greater than 7 days it is referred to as prolonged, refractory status epilepticus (PRSE). Limited information is available regarding the prognosis and management of PRSE.[2]

Lacosamide is a newly approved adjunctive treatment for partial onset epilepsy which has a novel mechanism of action that may underlie its effectiveness in intractable epilepsy. Lacosamide's effect in refractory status epilepticus has not been assessed in clinical trials.

2. Case report

An 8 year old boy with a mild learning disability was found in a convulsive seizure after 2 days of a mild febrile illness. He was treated with lorazepam followed by phenytoin loading and clinical convulsions resolved but encephalopathy persisted. Initial EEG showed slowing with no epileptic activity but the following day EEG showed frequent partial onset seizures. Treatment with phenytoin, phenobarbital, valproic acid, and leviteracetum did not abort the seizures. Propofol was added and titrated to induce a burst suppression pattern but when discontinued status epilepticus recurred. On the sixth day of persistent status epilepticus pentobarbital was titrated to induce burst suppression and he was transferred to our academic tertiary care hospital.

Examination upon presentation was significant for a mild skin eruption and a pleural effusion. Neurological examination showed decreased alertness and responsiveness with no focal signs. On presentation routine chemistries and CSF studies were normal as were brain CT and MRI. EEG initially showed a burst suppression pattern but when tapered off pentobarbital he had frequent, bilaterally independent, multifocal partial onset seizures. Initially he had subtle behavioral changes during the electrographic seizures but subsequently had minimal behavioral accompaniment. Extensive etiologic evaluation excluded traumatic, vascular, infectious, toxic and metabolic causes of status epilepticus. Brain biopsy 3 weeks after presentation showed mild nonspecific reactive changes. Elevated voltage gated potassium channel (VGKC) and thyroid peroxidase antibodies and elevated CSF IgG index suggested a potential immune etiology for the encephalopathy. Extensive investigations failed to uncover an occult malignancy.

There was a history of mild learning disabilities that was not formally evaluated but he had otherwise been typically developing and had no significant past medical or family history. There was no recent history of exposure to medications or toxins and no history of significant trauma.

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Combinations of phenytoin, levetriacetam, phenobarbital, topiramate, felbamate and valproic acid were tried over 10 weeks without success. Propofol, pentobarbital, midazolam, and ketamine were employed to induce a burst suppression EEG pattern for periods up to 1 week but SE resumed as soon as they were tapered. Ketogenic diet was started 6 weeks after presentation but provided no apparent benefit. He was treated with high dose corticosteroids, IVIG and plasmapheresis for a potential immune etiology. Repeated testing for anti-VGKC antibodies after this treatment was negative but there was no apparent clinical improvement. Trials of vitamin B6, folinic acid, carnitine, and biotin produced no response.

By the 10th week of PRSE he was being treated with a combination of 6 antiepileptic agents and still having over 300 partial-onset electrographic seizures per day identified on video EEG monitoring. At that point, 4 weeks after the last addition of a new AED, we started treatment with enteral lacosamide 25 mg twice daily. Within 3 days seizure frequency decreased significantly and by five days after initiation of lacomamide therapy EEG showed complete resolution of both electrographic seizures and interictal spikes.

After cessation of the PRSE the child showed increased alertness and awareness and he displayed some purposeful movements but no response to commends. Three months later he remained seizure free and was showing improvement in attentiveness and interaction but remained non-verbal and non-ambulatory.

3. Discussion

Status epilepticus may produce significant morbidity and mortality while RSE/PRSE is associated with an even poorer prognosis. There are no guidelines for the management of RSE/PRSE and few agents have been studied in prospective controlled trials so there is limited data to guide therapy.[1,3] Use of combinations of AEDs, anesthetic agents, ketogenic diet and surgical interventions has been described in case series.[2,4] Some authors suggest a poorer outcome with propofol use[2] but in the absence of randomized trials no agent can be considered as clearly effective.

Lacosamide was approved in Europe and in the US in adult patients as an adjunctive treatment of partial-onset seizures. It is a functionalized amino acid molecule and is the only agent in clinical use that is known to selectively promote the slow inactivation of voltage-gated sodium channels (VGSC).[5] Unlike other anticonvulsant drugs that affect VGSC, lacosamide has no effect on fast inactivation.[6] Functional interaction with collapsin-response mediator protein 2 (CRMP2) is another unique potential mode of action of lacosamide.[7] Lacosamide has a favorable pharmacokinetic profile, excellent bioavailability, minimal protein binding, few drug–drug interactions and experimental and clinical studies suggest a favorable safety profile.[5] Clinical trials in adults have demonstrated efficacy in treating partial onset epilepsy. Lacosamide has been shown to be effective in animal models of status epilepticus and potential neuroprotective properties have also been reported.[8] Although no clinical studies have evaluated the efficacy of lacosamide in status epilepticus, two recent cases of lacosamide use in adult patients with status epilepticus have been published. In one case lacosamide was effective after a first-line drug had failed[9] and in the second case after first and second-line anti-seizure therapies had failed.[10]

This child presented with pharmacoresistent PRSE, no history of epilepsy and the etiology remains inconclusive with only a few laboratory abnormalities. Evaluations failed to identify a cause of the symptomatic seizures and the etiology of the mild learning disability. He showed no dysmorphic features and both imaging and extensive metabolic workup were normal. He was found to have three markers of autoimmune response: elevated anti-voltage-gated potassium channel (VGKC), anti-thyroid peroxidase antibodies and elevated CSF IgG index. VGKC autoimmunity manifests with a wide spectrum of neurologic manifestations including cerebral cortical manifestations such as seizures and cognitive decline, hypothalamic, extrapyramidal, cerebellar, brain stem, spinal cord, peripheral neuropathy, and autonomic nerve system dysfunction.[11] In patients with anti-VGKC antibodies other organ-specific autoanbtibodies were found in 49% of the patients including thyroid immune disorders in 21%.[11] It was suggested that anti-VGKC antibodies may not be directly responsible for all neurologic manifestations but may be a marker for autoimmune neurologic disease, perhaps mediated by accompanying antibodies or cytotoxic T-lymphocytes. While seizures are common in patients with anti-VGKC antibodies, we found no report of anti-VGKC presenting with PRSE. Anti-thyroid peroxidase antibodies were mildly elevated but failure to respond to steroid treatment makes Hashimoto's Encephalopathy unlikely.

We believe that our case has similarities to a recently proposed clinical syndrome of childhood onset catastrophic epileptic encephalopathy that has been reported under various names including the most recently suggested acronym FIRES: febrile infection responsive epileptic encephalopathies of school age.[12] Children of school age with no prior seizure disorder or significant neurological history develop seizures and an acute encephalopathy following a nonspecific febrile prodrome. Within several days this progresses to prolonged, pharmacoresistant, partial onset SE. Prognosis has been universally poor and no effective therapy has been identified. Neuropathology shows minimal cellular inflammation similar to the biopsy in our patient. No specific etiology has been identified but autoantibodies have been reported in some.[13,14] It has been hypothesized that autoantibodies directly induce neuronal excitation leading to the epileptic phenomenon.[13] The autoantibodies and abnormal CSF IgG index in our patient also suggests activation of the immune system as a potential mechanism for his illness.

It is possible the resolution of our patient's seizures was unrelated to the addition of lacosamide although the total cessation of extremely frequent seizures after such a long duration and in close temporal relationship to the addition of the drug makes this unlikely. It is possible that the novel anti-seizure mechanism of lacosamide leads to a special effectiveness in PRSE. Further studies are required to evaluate lacosamide in the pediatric age group and to confirm this observation.

Our observation adds to the clinical data on use of lacosamide in pediatric patients and in patients with RSE or PRSE. Because of a favorable safety profile, an available intravenous preparation and in view of the dramatic success in our case we would recommend early consideration of lacosamide in future cases of refractory status epilepticus.

Conflicts of interest

None of the authors has any conflict of interest to disclose.

References

1. Lowenstein D. The management of refractory status epilepticus: an update. *Epilepsia* 2006;**47**(Suppl. 1):35–40.
2. Cooper A, Britton J, Rabinstein A. Functional and cognitive outcome in prolonged refractory status epilepticus. *Arch Neurol* 2009;**66**:1505–9.
3. Appleton R, Macleod S, Martland T. Drug management for acute tonic–clonic convulsions including convulsive status epilepticus in children. *Cochrane Database Syst Rev* 2008:CD001905.
4. Wusthoff C, Kranick S, Morley J, Christina Bergqvist A. The ketogenic diet in treatment of two adults with prolonged nonconvulsive status epilepticus. *Epilepsia* 2010;**51**:1083–5.
5. Harris J, Murphy J. Lacosamide: an adjunctive agent for partial-onset seizures and potential therapy for neuropathic pain. *Ann Pharmacother* 2009;**43**:1809–1817.

6. Errington A, Stöhr T, Heers C, Lees G. The investigational anticonvulsant lacosamide selectively enhances slow inactivation of voltage-gated sodium channels. *Mol Pharmacol* 2008;**73**:157–69.
7. Beyreuther B, Freitag J, Heers C, Krebsfänger N, Scharfenecker U, Stöhr T. Lacosamide: a review of preclinical properties. *CNS Drug Rev* 2007;**13**: 21–42.
8. Bialer M, Johannessen S, Levy R, Perucca E, Tomson T, White H. Progress report on new antiepileptic drugs: a summary of the Ninth Eilat Conference (EILAT IX). *Epilepsy Res* 2009;**83**:1–43.
9. Kellinghaus C, Berning S, Besselmann M. Intravenous lacosamide as successful treatment for nonconvulsive status epilepticus after failure of first-line therapy. *Epilepsy Behav* 2009;**14**:429–31.
10. Tilz C, Resch R, Hofer T, Eggers C. Successful treatment for refractory convulsive status epilepticus by non-parenteral lacosamide. *Epilepsia* 2010;**51**:316–7.
11. Tan KM, Lennon VA, Klein CJ, Boeve BF, Pittock SJ. Clinical spectrum of voltage-gated potassium channel autoimmunity. *Neurology* 2008;**70**:1883–90.
12. van Baalen A, Stephani U, Kluger G, Häusler M, Dulac O. FIRES: febrile infection responsive epileptic (FIRE) encephalopathies of school age. *Brain Dev* 2009;**31**:91. [author reply 92–93].
13. Okanishi T, Mori Y, Kibe T, Takahashi Y, Saito Y, Maegaki Y, et al. Refractory epilepsy accompanying acute encephalitis with multifocal cortical lesions: possible autoimmune etiology. *Brain Dev* 2007;**29**:590–4.
14. Sakuma H. Acute encephalitis with refractory, repetitive partial seizures. *Brain Dev* 2009;**31**:510–4.