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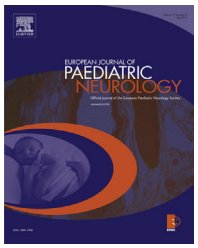

Original article

Lacosamide in children with refractory status epilepticus. A multicenter Italian experience

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ABSTRACT

Objective: Status epilepticus (SE) is considered a life-threatening medical emergency. First-line treatment with antiepileptic drugs (AEDs) consists of intravenous benzodiazepines followed by phenytoin. SE is considered refractory (RSE) when unresponsive to standard doses of the first two AEDs. Scarce evidence is available to support specific guidelines for the management of RSE in either adults or children. This study aimed to assess the efficacy and tolerability of intravenous (iv) lacosamide (LCM) in children affected by RSE.

Method: Children with RSE who were treated with ivLCM were included in the study. Efficacy was defined as the cessation of seizures after administration of ivLCM, with no need for any further antiepileptic drug. All patients had been unsuccessfully treated following standard protocols before ivLCM was administered.

Results: Eleven children entered the study (mean age: 9.4 years). Etiology was symptomatic in 7 patients (63%). RSE was convulsive (focal or generalized) in 6 patients and non-convulsive in 5. The mean initial bolus dose of LCM was 8.6 mg/kg. The drug, which was used as a fourth or later option, was effective in stopping RSE in 45% of patients, with seizures terminating within 12 h in three children. No serious adverse events attributable to LCM were reported.

Conclusions: LCM might be an effective and well-tolerated AED in children with RSE.

1. Introduction

Status epilepticus (SE) is a life-threatening emergency defined as an "acute epileptic condition characterized by continuous seizures for at least 30 min, or by 30 min of intermittent seizures without full recovery of consciousness between seizures".[1] The therapeutic approach includes (i) life support measures, (ii) identification and treatment of the etiologic cause, and (iii) rapid treatment with intravenous antiepileptic

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drugs (AEDs). First-line AEDs for SE consist of intravenous benzodiazepines (BDZ) followed by phenytoin (PHT) or fosphenytoin.[2–8] Two randomized controlled trials evaluated the effectiveness of lorazepam (LZP) in the first stage of SE and noted that only 65% and 59% of seizures were adequately controlled with benzodiazepines, respectively.[9] Therefore, at least one third of patients with SE could be expected to require second stage treatment with intravenous AEDs. SE is considered refractory (RSE) when unresponsive to standard doses of the first two AEDs used in therapy.[10,11] RSE may persist for more than 7 days, in which case it may be referred to as prolonged RSE.[12] When considered globally 10–40% of SE may evolve to a refractory state.[11,12] Data on the long-term prognosis of RSE are scarce.[10–12] Little evidence is available to support specific guidelines for the management of RSE.[10–13] Recent recommendations for adults suggest that the aggressiveness of treatment for RSE should be tailored to the clinical situation. A conservative approach might be adopted in focal motor RSE without impairment of consciousness. In contrast, the early induction of pharmacological coma is suggested in patients with generalized convulsive forms of the disorder. In the absence of evidence from randomized controlled clinical trials no agent can be considered as certainly effective.[14–17] Non-pharmacological approaches such as electroconvulsive therapy, hypothermia, or the ketogenic diet have also been used in RSE.[11,12,16]

Lacosamide (LCM) is a newly approved adjunctive treatment for partial onset seizures with a novel mechanism of action that may underlie its effectiveness in intractable epilepsy.[18] LCM has been reported to be effective in adult SE,[14,15] although data regarding pediatric patients are still scarce.

2. Patients and methods

We retrospectively analyzed data for all pediatric patients given intravenous LCM to treat RSE in three Italian centers between January 2011 and December 2012. All patients entering the study were placed under LCM as an add-on therapy in the treatment of established RSE. The drug was added to the medications administered as part of a standard protocol, including a sequence of BZD, PHT, valproic acid (VPA) and/or phenobarbital (PB), and levetiracetam (LEV). Drugs such as propofol and sodium thiopentone were also used in some cases. Patient medical charts were carefully reviewed. Electrophysiological data and clinical findings were recorded, including: sex, age, etiology, epilepsy history, seizure type, onset and duration of SE, order in which AEDs were administered, loading and maintenance doses of intravenous and concomitant AEDs, as well as responsiveness and adverse events during LCM therapy. All patients underwent continuous EEG monitoring at the time of LCM initiation and for a minimum of 48 h following the initial dose. SE was diagnosed according to the following criteria: (a) any seizure lasting for 30 min or longer, or (b) intermittent seizures repeating within 30 min without full recuperation of consciousness.[1] SE was classified according to semiology and divided into convulsive SE (focal motor or generalized) or nonconvulsive SE, based on EEG features.[6–8] RSE was defined as status epilepticus with a failure to respond to standard doses of at least two medications.[9–12]

Cessation of RSE was defined as the disappearance of EEG seizure activity (all patients with a diagnosis of nonconvulsive RSE underwent continuous EEG monitoring) or the disappearance of previous ictal symptoms without any suspicion of ongoing subclinical seizure, if confirmed by a subsequent EEG recording. We considered RSE as under control if no change in antiepileptic medication was needed for at least 48 h after clinical or electrographic resolution. The last AED administered before RSE cessation was defined as the termination drug, regardless of the latency between its first administration and RSE cessation. Analysis of adverse reactions included evidence of hypoventilation, hypotension, cardiac dysrhythmia, fever, and laboratory abnormalities. Routine blood tests were performed regularly. The Institutional Review Board of each epilepsy unit approved the study; no support was received from pharmaceutical companies.

3. Results

Eleven patients were included in the study. Six (54%) patients had convulsive RSE, and five (46%) had nonconvulsive RSE. Clinical findings are reported in Table 1. When considered globally, the patients were aged 3–16 years (mean 9.4 years). Etiology was unknown in 37% of cases. Structural/metabolic causes were present in the remaining group of patients (Table 1). Nine (81%) patients had a previous history of epilepsy and had received a median of two AEDs. When SE occurred, the antiepileptic drugs administered included: VPA (5 patients, mean dose 34.1 ± 6.2 mg/kg/day; mean plasma level 88.3 ± 4.8 μg/ml), carbamazepine (4 patients, mean dose 8.1 ± 1.1 mg/kg/day; mean plasma level 8.2 ± 1.9 μg/ml), topiramate (4 patients, mean dose 5.6 ± 0.4 mg/kg/day, plasma levels not available), vigabatrin (4 patients, mean dose

Table 1 – Clinical findings and baseline data.

	CRSE ($n = 6$)	NCRSE ($n = 5$)
Mean age (years)	9.6	9.1
Sex (M/F)	3/3	2/3
Prior history of epilepsy	5 (83%)	4 (80%)
Etiology		
Unknown	3	1
Structural/metabolic		
Neuronal migration disorders	2	–
PRES	–	1
Cerebral palsy	1	2
Encephalitis	–	1
LCM loading dose (mg/kg): mean (range)	8.8 (6.9–9.9)	8.3 (6.7–9.5)
LCM maintenance dose (mg/kg/day): mean (range)	12.9 (9.1–13.9)	11.9 (8.8–13.4)
Time from seizure onset to LCM therapy: mean (range)	52.5 h (22–576)	63.5 h (31–90)
AEDs before RSE: mean (range)	3.1 (2–6)	2.8 (2–5)

CRSE: convulsive refractory status epilepticus; NCRSE: nonconvulsive status epilepticus; PRES: posterior reversible encephalopathy syndrome; LCM: lacosamide; AED: antiepileptic drugs.