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ORIGINAL RESEARCH ARTICLE

Safety and Efficacy of Intravenous Lacosamide for Adjunctive Treatment of Refractory Status Epilepticus: A Comparative Cohort Study

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Abstract
Background Refractory status epilepticus (RSE) is an emergency with high mortality requiring neurointensive care. Treatment paradigms include first-generation antiepileptic drugs (AEDs) and anesthetics. Lacosamide (LCM) is a new AED, holding promise as a potent treatment option for RSE. High-level evidence regarding safety and efficacy in the treatment of RSE is lacking.
Objective The objective of the study was to evaluate the safety profile and efficacy of intravenous (i.v.) LCM as an add-on treatment in adult RSE patients.
Methods All consecutive RSE patients treated in the intensive care units (ICUs) of an academic tertiary care center between 2005 and 2011 were included. Severity of status epilepticus (SE) was graded by the SE Severity Scale (STESS), and SE etiology was categorized according to the guidelines of the International League Against Epilepsy (ILAE). Outcomes were seizure control, RSE duration, and death.
Results Of 111 RSE patients, 53 % were treated with LCM. Twenty-five patients with hypoxic-ischemic encephalopathy were excluded. Mortality was 30 %. Mean number of AEDs, duration, severity, and etiology of SE, as well as critical medical conditions did not differ between patients with and without LCM. While age tended to be higher, critical interventions, such as the use of anesthetics and mechanical ventilation, tended to be less frequent in patients with LCM. Seizure control tended to be achieved more frequently in patients with LCM (odds ratio, OR 2.34, 95 % CI 0.5–10.1, $p = 0.252$). Among patients with LCM, 51 % received LCM as the last AED (including hypoxic-ischemic encephalopathy), allowing the reasonable assumption that LCM was responsible for seizure control, which was achieved in 91 %. Multivariable analysis revealed a decreased mortality in patients with LCM (OR 0.34, 95 % CI 0.1–0.9, $p = 0.035$). A possible confounder in this context was the implementation of continuous video-electroencephalography (EEG) monitoring 6 months prior to the first use of i.v. LCM. There were no serious LCM-related adverse events.
Conclusion LCM had a favorable safety profile as adjunctive treatment for RSE. Its use was associated with decreased mortality of RSE—a finding that might have been confounded by the implementation of continuous video-EEG monitoring in the ICU prior to the use of i.v. LCM, leading to heightened awareness as well as earlier diagnosis and treatment of SE. Randomized trials are warranted to further strengthen the evidence of efficacy of LCM for RSE treatment.

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1 Introduction

Status epilepticus (SE) is the most severe manifestation of epilepsy, which requires intensive care. Its incidence ranges from 15 to 20 per 100,000 per year [1, 2]. Several treatment guidelines for SE suggest a four-step algorithm depending on the persistence of SE [3–6]. Briefly, benzodiazepines are recommended as first-line antiepileptic drugs (AEDs), followed by one further intravenous (i.v.) second-line AED if SE persists, such as phenytoin, valproic acid, a combination of both, or levetiracetam. For further ongoing seizure activity non-sedating third-line AEDs are often used, followed by anesthetic drugs to induce a deep coma titrated at least to burst-suppression or even flat-line electroencephalography (EEG). However, the latter is only based on recommendations [7, 8]. Without prompt interventions, ongoing seizures can cause deleterious neuronal injury or death [9]. This causality is underscored by the association of treatment failure and unfavorable prognosis with increasing SE duration [10]. Failure of first-line AED and second-line treatment with at least one i.v. AED defines refractory status epilepticus (RSE) [11], which is found in up to 43 % of patients with SE and is predominantly associated with fatal underlying etiologies, severe impairment of consciousness, and a mortality rate of up to 40 % [12–14]. Therefore, rapid treatment escalation is essential. The importance of extensive therapeutic intervention in these patients is further emphasized by reported favorable outcomes after extensive long-term RSE treatment [15]. To date, treatment escalation in RSE remains challenging as interactions and adverse effects of multiple co-administrated drugs are hazardous, and effective add-on treatment options are limited. Thus, novel treatment options with new targets and additional modes of action with less adverse effects and risks would be highly welcome.

Lacosamide (LCM) (SPM 927, formerly harkoseride), the *R*-enantiomer of 2-acetamido-*N*-benzyl-3-methoxypropionamide, is a promising new AED approved in 2009 with enteral and i.v. formulations. It has a bimodal action and almost no interactions. The selective enhancement of the slow inactivation of voltage-gated sodium channels may help normalize activation thresholds and decrease pathophysiological neuronal activity [16, 17]. Uncoupling of the collapsin-responsive mediator protein-2 from the presynaptic Ca^{2+} channel complex may contribute to the decreased neuronal loss [18, 19] and may provide some neuroprotective effect. LCM has been shown to reduce seizure frequency in patients with uncontrolled partial-onset seizures [20] and i.v. LCM has a comparable safety profile and tolerability to those of oral formulations when used as replacement therapy for patients with partial-onset seizures [21]. Aside from induction of atrial flutter, reported PQ interval prolongation on the electrocardiogram (ECG) in a dose-dependent manner and clinically relevant atrioventricular block, in one case associated with high doses of LCM [22–24], no severe adverse effects or significant laboratory abnormalities were shown to be associated with LCM. Interactions of LCM with plasma concentrations of other AEDs could not be demonstrated in vivo so far [20]. A few studies reported on LCM for the treatment of SE [25]. The use of LCM in RSE has been described in some case reports [26, 27] and smaller case series [28–30]. Randomized controlled trials on the efficacy of LCM in RSE are lacking and not registered in the National Institutes of Health (NIH)-sponsored database (clinicaltrials.org), possibly because of ethical restrictions in these critically ill patients.

The aim of this study was to explore the feasibility, efficacy, safety profile, and effect on outcome of i.v. LCM in a large cohort of critically ill adult patients suffering from RSE.

2 Methods

2.1 Setting and Study Design

This retrospective comparative cohort study was performed at the University Hospital Basel (Switzerland), a tertiary care center with more than 4,000 intensive care unit (ICU) admissions per year. On the basis of the hospital's policy, all patients with SE were treated in the ICU. The study was approved by the local ethics committee in accordance with the standards laid down in the 1975 Declaration of Helsinki, as revised in 2000 (World Medical Association Declaration of Helsinki 2000). The requirement for informed consent was waived.

2.2 Patients and Data Collection

We identified all consecutive adult patients with RSE in the medical, cardiac, and surgical ICUs between January 2005 and December 2011 by searching the medical records and the EEG database of the University Hospital Basel. All RSE patients had to have no prior treatment with i.v. LCM. We decided to present the individual detailed information of all patients who received LCM, including patients with hypoxic-ischemic encephalopathy as electronic supplemental material, as we believe that treatment experience in this distinct group should not be withheld. However, we excluded them from all multivariable analyses, as this etiology of RSE is considered to be different from other causes, owing to the largely irreversible brain damage and poor outcome [31–34]. At our institution, treatment of SE was standardized according to the guidelines of the Swiss

Status Epilepticus Consensus Conference from 2005 [3, 35]. Briefly, benzodiazepines were applied as first-line AEDs when there was high suspicion of SE or immediately after SE diagnosis, followed by one further i.v. second-line AED if SE persisted, such as phenytoin, valproic acid, a combination of both, or levetiracetam. Anesthetics or non-sedating third-line AEDs were applied after failure of first- and second-line AEDs. LCM was administered after failure of first- and second-line AEDs and in selected patients as the second drug, based on the treating neurologist's judgment. In 2009 i.v. LCM was introduced as an add-on AED for the treatment of SE in our hospital. No patients with SE were treated with LCM before April 2009. Of note, while not all patients with SE were treated with LCM, all consecutive patients with RSE were treated with LCM as an add-on AED from May 2009 to December 2011. i.v. LCM twice a day with 200 mg per application without an initial 'loading dose'. Patients with renal failure received 150 mg twice daily (b.i.d.) (creatinine clearance 30–50 ml) or 100 mg b.i.d. (creatinine clearance less than 30 ml); one obese patient (110 kg) was treated with 600 mg per day.

Aside from characteristics that allow gradation of SE severity and duration (as mentioned in Sect. 2.3), etiologies of RSE [including hypoxic-ischemic encephalopathy], critical medical conditions, such as infections during SE, information from continuous ECG monitoring during the ICU stay, mechanical ventilation, and the use of anesthetic drugs during SE were compiled for all patients. Data on the exact sequential arrangement of all AEDs and i.v. anesthetic drugs were assessed for all patients treated with and without LCM.

2.3 Status Epilepticus: Definition, Categorization, and Graduation of Severity

SE was diagnosed if seizures lasted at least 5 min or if a series of seizures emerged without recovery of mental status in between [36–38]. RSE was defined as SE refractory to first-line AEDs and second-line treatment with at least one i.v. AED [11]. These widely accepted definitions allow a comparison with previous works on RSE treatment. Regarding etiologies of SE, seizures were categorized as recommended by the International League Against Epilepsy (ILAE) [39] as follows: acute symptomatic seizures, remote symptomatic unprovoked seizures, symptomatic seizures due to progressive CNS disorders, and unprovoked seizures of unknown etiology. Severity of SE was graded using the validated Status Epilepticus Severity Score (STESS) [40, 41]. According to this, the following integral components of STESS were used and categorized as follows: worst seizure types at presentation (simple partial, complex partial, and absence seizures = 0 points; generalized convulsive seizures = 1 point; and nonconvulsive status epilepticus (NCSE) in coma = 2 points), history of prior seizures (0 points) or no history of seizures (1 point), age of at least 65 years (2 points) and less than 65 years (0 points), and level of consciousness at SE onset (awake or somnolent = 0 points; stuporous or comatose = 1 point). Duration of SE was defined as the period from the time of SE diagnosis to the time when SE stopped. Seizure control was confirmed if there was no evidence of clinical manifestations and seizure activity on EEG. All patients had at least one routine EEG at admission, and follow-up recordings with at least two conventional EEGs in 24 h or continuous EEG monitoring were performed in all patients without seizure control.

2.4 Outcomes

Primary outcomes were SE duration, seizure control, and death. Secondary outcomes included destination at discharge. Safety was defined as the absence of adverse events, signs, or symptoms like rash, blood dyscrasias, impairment of cardiovascular, renal, liver, and pulmonary function closely related to the administration of LCM and requiring acute medical intervention.

2.5 Statistics

Patients with hypoxic-ischemic encephalopathy were excluded from all comparative analyses, as mentioned above [31–34]. Patients were categorized into the following two groups: with and without treatment with i.v. LCM during RSE. Categorical variables were summarized as counts and proportions and continuous variables as means and standard deviations. The Shapiro–Wilk test was used to distinguish between normal and non-normal distributions. Continuous variables were analyzed with the Student's t test if normally distributed, or the Mann–Whitney U test if non-normally distributed. For comparisons of proportions, Chi-square and Fisher's exact test were applied where appropriate. Robust multiple linear regression models were fitted using bootstrapped interactively re-weighted least squares with 1,000 replications to reduce the effects of extreme or non-normal 'RSE duration' data. Univariable logistic regression was used to determine differences in categorical outcomes for patients with and without treatment with i.v. LCM. A multivariable logistic regression model was used to adjust for age. Hosmer–Lemeshow goodness-of-fit tests were applied to check the multivariable logistic regression models. p values of 0.05 and less were considered significant. Statistical analysis was performed with STATA® version 12.0 (Stata Corporation, College Station, TX, USA).

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