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Intravenous lacosamide (LCM) in status epilepticus (SE): Weight-adjusted dose and efficacy

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ABSTRACT

Background: Some studies suggest higher efficacy of lacosamide (LCM) in status epilepticus (SE) with higher loading doses; however, this weight-adjusted dose has not been evaluated.
Objective: The objective was to evaluate the relationship between loading weight-adjusted dose and efficacy of LCM in SE.
Methods: A group of patients with SE treated with LCM from Spanish hospitals was examined retrospectively. Demographic data, type of SE, etiology, response rate, last antiepileptic drug (AED) used, treatment line in which LCM was used, total loading dose, and weight-adjusted dose were collected.
Results: One hundred sixty-five cases of SE were collected; 87 (52.7%) patients had nonconvulsive SE. Mean age was 64.2 ± 17.2 and 60.6% (n = 100) were men. Regarding etiology, SE was considered as acute symptomatic in 85 (51.5%), remote symptomatic in 51 (30.9%), progressive symptomatic in 10 (6.1%), and cryptogenic in 19 (11.5%). Lacosamide was used as the third drug in 46.1%, and as a second option in 28%. In 115 patients, clonazepam had been used as the first option, and no benzodiazepines had been administered in the remaining 50. The median loading dose was 400 mg (100–600 mg), and the weight-adjusted dose was 5 mg/kg (3–6 mg/kg). The response rate was 63.3%, and 55.1% responded within the first 12 h.
Efficacy was significantly higher in patients who had taken benzodiazepines at LCM loading doses >5.3 mg/kg (p = 0.006). This relationship was maintained independent of using other concomitant AEDs. However, if benzodiazepines were not taken, this relationship was not found.
Conclusions: In adults with benzodiazepine-resistant SE, the response rate to LCM was higher, with weight-adjusted doses above 5.3 mg/kg.

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1. Introduction

The intravenous formulation of lacosamide (LCM) is bioequivalent to the oral preparation and presents good tolerability [1–3]. This is why its use for the treatment of seizure clusters and status epilepticus (SE) was initiated. Up to 21 series of patients and isolated case reports have been published in which a variable efficacy has been shown, and a systematic review of the current evidence has recently been conducted taking into account these series, showing an efficacy rate between 57 and 61% according to the type of SE (reaching up to 92% in cases of focal motor SE) [4]. These series include use not only in the adult population but also in the pediatric population.

Concerning the intravenous formulation of LCM, safety has been reported in the loading dose of up to 400 mg in patients with focal epilepsy [3], and the published series collected and summarized in the study by Strzelczyk et al. [4] report that the most commonly used loading dose is between 200 and 400 mg. However, the optimal dose for cluster treatment or status epilepticus has not been clearly defined, if we also take into account that LCM was recently licensed for daily doses of 600 mg in monotherapy.

Some studies point to a trend towards greater efficacy or a faster early response with higher doses [5,6], but these data have not been corroborated in a significant way. One of the reasons that could explain

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this failure to corroborate greater efficacy at total dose could be the lack of adjustment of the dose to weight, which would mean different plasma concentrations for each patient with the same loading dose. Only adjusted doses in pediatric series between 2 and 10 mg/kg have been reported [7–10].

More recently, Ramsay et al. [11] have shown that high weight-adjusted doses (10–12 mg/kg) at an infusion rate of 0.4 mg/kg/min can be administered safely; with this regimen, the plasma levels considered as reference would be reached. Based on these data, our aim was to ascertain the LCM weight-adjusted intravenous loading dose which is related to the greatest efficacy, in a manner similar to that defined for the remaining antiepileptic drugs (AEDs).

2. Methods

A multicenter study of 7 Spanish hospitals was conducted in which cases of patients older than 16 years of age with SE, and who received intravenous LCM for their treatment, were collected prospectively between January 2013 and February 2017. Patients with postanoxic etiology were excluded. This registry received approval from our local ethics committee.

The demographic profile (sex, age) and the presence of previous seizures were collected prospectively at admission.

With regard to SE, the worst type of seizure that patients presented in each episode was initially collected and retrospectively adapted following the latest proposal from the International League Against Epilepsy (ILAE) classification of SE [12], with prominent motor symptoms including generalized convulsive status epilepticus (GCSE), myoclonic or focal motor SE, and SE without prominent motor symptoms including nonconvulsive SE (NCSE) in coma and focal with and without deterioration in the level of consciousness.

The etiology of SE was determined based on the ILAE classification (acute, remote, progressive symptomatic, or cryptogenic) [12]. In addition, the etiology was classified as "potentially fatal etiology" (PFE) which can lead to death if not treated specifically (independent of SE). This follows the definition of other publications [13].

The modified SE severity score (mSTESS) was calculated for each patient at admission [14].

Regarding the treatment, all treatment lines and the number of AEDs used were collected, as well as the need to administer intravenous anesthetic drugs (IVAD). Refractoriness was defined when more than two treatment lines were used at appropriate doses (benzodiazepines + AED or AED + AED).

The response to treatment in these patients was monitored clinically and with an electroencephalography (EEG) to verify the disappearance of continuous epileptic activity. Electroencephalography monitoring was performed at intervals in most of the cases; as this is a multicenter study, continuous EEG was not available in some of the hospitals. The response rate to treatment and AEDs administered prior to SE resolution were collected. Efficacy was defined as the last drug introduced into the antiepileptic therapy or increased in dose within 24 h before termination of the SE without changes in the comedication; this criterion has been reported as the most appropriate measure for the evaluation of efficacy of an AED in the treatment of SE [15]. The order in which LCM was used, the total loading dose, and the weight-adjusted dose were considered.

Informed consent was obtained from all individuals or from legal authorized representatives of all participants included in the study in order to analyze the different clinical variables collected.

2.1. Statistical analysis

Descriptive and frequency statistical analyses were obtained, and comparisons were made using the software SPSS Statistics 22.0.

Statistical significance for intergroup differences was assessed using Pearson's chi-square test or Fisher's exact text for categorical variables and using Student's *t*-test or Mann–Whitney *U* test for continuous variables. Receiver operating characteristic (ROC) curves were configured in order to calculate cutoff points for weight and weight-adjusted dose with greatest sensitivity and specificity to predict good efficacy. Multivariate analyses were performed using logistic regression models to identify the independent predictors of good efficacy. A p-value of <0.05 was considered statistically significant.

3. Results

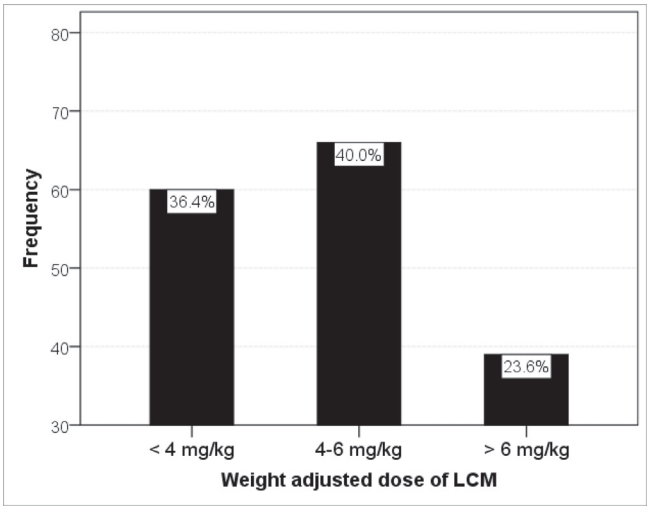
In that time, a total of 165 cases of patients with SE treated with LCM were collected. The mean age was 64.2 ± 17.2 and 60.6% (n = 100) were men. A total of 76 patients (46.1%) had a history of epilepsy. Regarding the etiology, SE was considered as acute symptomatic in the majority (n = 85; 51.5%), delayed symptomatic in 51 (30.9%), and progressive symptomatic in 10 (6.1%); finally, the remaining 19 (11.5%) had SE that was considered as cryptogenic. With regard to semiology, slightly more than half (n = 87; 52.7%) had SE with no prominent motor symptoms; of the rest (n = 78), most (n = 59; 35.8% of the total) had focal motor SEs. Four patients were readmitted with LCM used in every episode of SE.

Regarding the treatment of the sample, SE in 144 patients (87.3%) was considered refractory because these patients needed more drugs after their condition failed to respond to two treatment lines: LCM was effective in 105 patients (63.6% of the overall sample), and this response was complete within the first 12 h after its administration in 91 patients (55.2%).

The median loading dose used was 400 mg (100–600 mg), and the weight-adjusted dose was 5 mg/kg (3–6 mg/kg). If we observe the dose distribution, most patients received between 200 and 400 mg of total dose and between 4 and 6 mg/kg when adjusted by weight, as seen in Fig. 1.

Regarding safety, 16 patients had adverse effects attributed to LCM. These were of mild intensity in 14 (increased drowsiness in 9, diplopia in 2, vomiting in 1, blurred vision in 1, and increase in PR interval in 1) and more severe cardiac complications in 2: hypotension and bradycardia in 1 patient, and atrioventricular (AV) block in the other.

Lacosamide was used as the first option without previous benzodiazepines in 5 patients (3%). It was used in 38 patients (23%) as a second option, in 76 (46.1%) as the third option, in 35 (21.2%) as the fourth option, and in 11 (6.7%) as the fifth option. Overall, the efficacy was quite similar regardless of the order in which it was used (p = 0.350). Overall, in 115 patients, it was used following the treatment guidelines using clonazepam as the first option, and in the remaining 50, the



LCM: Lacosamide

Fig. 1. Distribution of loading doses of LCM (adjusted by weight).

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