Intravenous lacosamide in status epilepticus: correlation between loading dose, serum levels, and clinical response

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Abstract

Introduction: Intravenous lacosamide (LCM) is increasingly used in the treatment of status epilepticus (SE), but optimal loading dose and target serum levels are unclear. We analysed the correlation between LCM serum levels after intravenous loading dose and clinical response.

Materials and methods: Retrospective study in two centres from December 2014 to May 2016 including consecutive SE patients treated with LCM, in which trough serum levels after intravenous loading dose were available. Trough levels were correlated with the loading dose and the clinical response, defined as LCM introduction terminating SE without the need of further treatment. Correlations were adjusted for other SE characteristics.

Results: Among 40 patients, 16 (40%) responded to LCM. LCM serum concentrations within the reference interval (10-20mg/l) were associated with loading doses of >9mg/kg ($p=0.003$; $\chi 2$). However, we observed no difference between LCM serum levels in responders (median 10.4 mg/l) versus non-responders (median 9.5 mg/l; $p=0.36$; U-test), even after adjusting for other predictors of clinical outcome (SE severity, aetiology, and number of previous treatment).

Discussion: High intravenous LCM loading doses (>9 mg/kg) were associated with serum levels within the reference interval, there was however no correlation with the clinical response. These data question the benefit of increasing LCM loading doses in SE. Prospective studies are needed to evaluate the benefit of increasing the LCM loading dose in SE.

Keywords: retrospective; therapeutic drug monitoring; critical care; outcome

Highlights:

- LCM lacks a defined target serum levels after loading dose in SE.
- A loading dose of >9mg/kg is associated with serum levels above 10mg/l.
- Higher serum levels are not correlated with better clinical response in SE.

1. Introduction

Status epilepticus (SE) is a prolonged epileptic activity, secondary to the loss of mechanisms of seizure termination (Trinka et al., 2015); it represents a neurologic emergency with considerable morbidity and mortality (Betjemann and Lowenstein, 2015; Novy et al., 2010). Benzodiazepines constitute the first line of treatment, followed by intravenous (IV) antiepileptic drugs (AEDs) (Brophy et al., 2012; Glauser et al., 2016; Meierkord et al., 2010). IV AEDs are most commonly administered through a weight dependent loading dose to achieve efficient serum levels as quickly as possible.

Lacosamide (LCM) is available since 2008 with an IV formulation. In chronic epilepsy it is licensed up to 400mg daily for maintenance treatment; the proposed reference serum interval lies between 10 and 20mg/l (Patsalos, 2013). Dose adaptation is not required according to gender or comedications (Cawello, 2015). LCM represents a promising option for the treatment of SE: administered as intravenous loading dose it lacks major side effects (Fountain et al., 2013) and relevant pharmacological interactions (Cawello et al., 2014). Consequently, it is increasingly used “off-label” in this setting (Falco-Walter and Bleck, 2016; Kellinghaus et al., 2014), and has been evaluated in randomized control trial with pending results (Husain, 2015). However, ideal loading doses remain uncertain.

Boluses of 200-400mg are usually administered in SE (Höfler and Trinka, 2013), and a small prospective study suggested that 400mg could possibly prove more efficacious than 200mg (Legros et al., 2014). It was recently observed that loading doses of 8mg/kg (approximately 550 mg for a 70kg patient) were needed to reach a serum level within the reference interval (Ramsay et al., 2015) and that doses of more than 10-12mg/kg resulted in levels above 15 mg/l . Measurements of serum levels could represent a useful surrogate marker of exposition to ascertain the clinical response in SE. In this study, we assessed serum levels after IV LCM loading dose to explore their relationship with the clinical response.

2. Material and methods

2.1. Registry and patients selection

We carried out a retrospective analysis in two centres in Western Switzerland: CHUV (the University Hospital of Lausanne) and Sion (a large regional hospital) including all SE episodes treated between December 2014 (first available serum level in SE) and May 2016. All adults with SE in CHUV are registered in a prospective registry (Novy et al., 2010) that was approved by the relevant ethics committee; the Sion hospital started in June 2015 an identical database. Patients with suspected SE at both hospitals are referred for neurological consultation and EEG: both procedures are supervised by senior epileptologists (VA in Sion; AOR and JN at the CHUV), who proceed to the inclusion of all patients with confirmed SE (defined as a single seizure lasting more than five minutes, or multiple seizures without return to baseline) into the registries. EEG was available on a daily basis and monitoring was performed when needed. Episodes occurring in patients younger than 16 years old or post-anoxic SE are excluded because of significant differences in physiopathology and prognosis. Treatment follows an in-house protocol based on current guidelines (Brophy et al., 2012; Rossetti and Lowenstein, 2011). LCM is recommended as third line treatment and is thus mostly used for refractory cases.

2.2. Definition of variables

For each SE episode, patient characteristics (demographics, estimated body weight), SE features (potentially fatal aetiology as previously described (Rossetti et al., 2006)), the validated STESS prognosis score including age, consciousness before treatment, worst seizure type, occurrence of previous seizures (Kang et al., 2015; Rossetti et al., 2008; Raoul Sutter et al., 2013), survival at hospital discharge, and treatment characteristics (time, loading doses and sequence of AEDs) were prospectively recorded in the registries.

End of SE was defined as cessation of seizure activity and clinically determined by the neurologic consulting team; EEG confirmation was mandatory for non-convulsive SE forms (Novy et al., 2010). Based on the end of SE, we defined a clinical response to LCM if it was the last AED introduced before SE termination, regardless of timing. Patients who died while still in SE were considered non-responders.

For patients treated with loading doses of LCM, we routinely performed serum levels to adapt the maintenance treatment. Levels were determined using ultra-performance liquid chromatography - tandem mass spectrometry (Decosterd et al., 2015). The laboratory participates to an External Quality Proficiency Program for antiepileptic drugs (LGC Standards Proficiency Testing, Lancashire, BL9 OAP, United Kingdom). We retrospectively included every SE episode with an available LCM serum level. All serum levels measured less than six hours (peak level) or more than 36 hours after the loading dose were excluded to allow analysis of uniform trough serum levels. A reference of 10-20mg/l was used (Patsalos, 2013). Patients with more than one SE episode were only included for the first episode.

2.3. Statistical analysis

SE episodes were divided into two groups: responders to LCM versus non-responders. Statistical calculations to investigate the association between loading doses and serum levels and responder status were performed using *SPSS version* 23.0 (IBM corp., Armonk, NY). Chi-square, Fisher, Mann-Whitney U, and Spearman tests were applied as required for univariable analyses. A multivariable backward binary logistic regression was applied for identification of variables, including LCM serum levels, associated with the clinical response to LCM, after adjustment for potential confounders, such as relevant SE outcome predictors, such as SE severity (STESS), potentially fatal cause, and LCM position in the treatment sequence.

3. Results

3.1. Patients characteristics

We included 40 SE patients with LCM trough serum levels. Thirty-seven were treated at the CHUV and three in Sion. At the CHUV, the 37 included episodes with serum levels corresponded to 65% of 57 SE episodes treated with LCM during the same period. Among the 20 remaining episodes, seven had no available levels, 11 were excluded because LCM serum levels were collected more than 36 hours after the loading dose, and two other because the dosing was performed less than six hours after the last LCM administration. One episode was not included because it affected a patient previously included for another SE. Comparing the 20 excluded SE episodes with the included cases, response to LCM was 45%, similar to the 41% in included SE episodes (p=0.75, $\chi 2$). All other patient's characteristics were also similar: median age (67 versus 68 years, p=0.42, U test), gender (65% versus 43% men, p=0.12, chi-square), potentially fatal cause (75% versus 57%; p=0.17, chi-square), median position of LCM within the treatment (3^{th} in both groups, p=0.40, U-test), median STESS (3 versus 3, p=0.70, U test), and mortality at discharge (30% versus 11%, p=0.14, Fisher test).

Among the 40 analysed episodes, there were 19 men (48%), median age was 68 years (range 34-88 years), and median estimated body weight was 70 kg (range 45-92 kg). Worst SE semiology was generalised convulsive in 17 episodes (43%); 24 patients (60%) had a potentially fatal cause and five (13%) did not survive until hospital discharge. The median STESS score was 3 (range 0-6) and 12 patients (30%) had a favourable score of less than 3. No patient was included twice.

3.2. LCM loading dose and serum levels

The median LCM loading dose was 600 mg (range 100-800 mg) and increased over time from 400 mg (range 100-800) in the first 20 episodes (December 2014 to September 2015) to 600mg (range 200-800) in the last 20 (September 2015 to May 2016) (p=0.01; U test). When expressed relative to estimated body weight, loading dose corresponded to a median of 7.5 mg/kg (range 1.3-16).

The median LCM serum level was 10.0 mg/l (range 2.4-24.8 mg/l), meaning that 20 LCM levels (50%) fell within the 10-20 mg/l reference interval. Median time between the blood sampling and the loading dose was 15.9 hours (range 6.25-34.75 hours).

There was a correlation between serum levels and loading doses related to body weight ($p<0.001$, Spearman test) and when comparing the loading dose of the episodes within the reference range and those below ($p=0.002$; U test) (**figure 1**). A loading dose of 9 mg/kg or more was associated with levels within the reference range ($p=0.003$, $\chi 2$). There was a trend for this association regarding doses of more than 8 mg/kg ($p=0.057$, $\chi 2$). The highest LCM serum level was 24.8 mg/l, SE resolved in that patient, but she showed transient vertigo and nystagmus. No other adverse events were observed. Among the five deceased patients, three died while still in SE, the cause of death was considered to be unrelated to treatment.

3.3. Clinical response

Overall, 16 episodes (40%) responded to LCM. Comparison between responders and non-responders (**table 1**) shows no differences in demographics, potentially fatal cause, SE duration before LCM, median position of LCM within the treatment sequence and loading doses of LCM. The total number of AEDs was smaller and the time from LCM loading to SE cessation was shorter in the responder group ($p<0.001$ for both, U-tests). Non-responders also showed higher STESS ($p=0.04$, U test) and a trend towards higher mortality at discharge ($p=0.07$, Fisher). There were no association between LCM loading dose itself and response.

The distribution of LCM serum levels did not differ significantly when comparing responders and non-responders ($p=0.36$, U test) (**figure 2**). When correcting for confounders, the difference did not reach significance even after adjustment for STESS (OR: 1.14, 95% Confidence Interval (CI): 0.94-1.37; $p=0.18$), position of LCM in the treatment sequence (OR: 1.11; 95% CI: 0.95-1.30; $p=0.19$), or potentially fatal cause (OR: 1.13; 95% CI: 0.96-1.33; $p=0.15$).

4. Discussion

4.1. Relation between loading dose, serum levels and clinical response

This study confirms that, in adult patients with SE, LCM loading doses higher than 9mg/kg are neededto reach the reference range reported in people with chronic epilepsy. Treatment response was however neither significantly determined by the loading dose of LCM nor by the resulting serum level.

LCM use in SE is off-label and initial doses (200-400mg) are mostly derived from intravenous replacement for oral therapy; 400mg being the highest daily dosage approved. Given the LCM volume of distribution, fixed loading with 200 to 400mg seems insufficient to quickly reach levels within the reference range of 10-20mg/l: we indeed observed that doses of at least 9mg/kg (around 600mg for a 70kg patient) were needed to obtain such a target. This threshold is congruent with a recent report (Ramsay et al., 2015), where doses up to 1200mg were mentioned.

Our response rate of 40% is somewhat lower than in a review reporting similar dosages (Höfler and Trinka, 2013), and in which the overall success rate of LCM was 56%. This comparison is however limited by the heterogeneity of the criteria used to define drug response. Our findings are also surprising given the previous suggestion (Legros) that loading doses of 400mg are more efficacious than 400mg using the same response definition. We cannot exclude that there is an overall benefit of administering 400mg over 200mg, but our results question the benefit increasing further the loading dose. The lack of association between higher serum levels and better clinical response may have at least two possible explanations. First, the most important predictors of clinical outcome in SE are age and the underlying aetiology (R Sutter et al., 2013); the influence of treatment is probably smaller (Rossetti et al., 2013): the present study was probably underpowered to detect a small effect. Secondly, the 10-20mg/l interval was suggested as the equilibrium serum level in long-term treatment of epilepsy, and established in outpatients under commonly prescribed doses, with no defined reference to the medication response (Patsalos, 2013). It is not clear if the same range is applicable for SE, where most patients are critically ill. Although it seems reasonable to ascertain bioavailability in critical situation, the literature related to therapeutic drug monitoring in SE is extremely scarce, and target levels for newer AEDs in that setting are still

a matter of debate (Loh et al., 2010). It is relevant to note that there were no association between LCM loading dose itself and clinical response. Direct comparison between both variables thus did not unmask any correlation compared to analysis with serum levels.

Although such a conclusion can only be made in the presence of a prospective trial, the absence of tangible clinical effects when increasing the LCM loading dose may questions exposing patients to unnecessary adverse events. In our cohort, the treatment was generally well tolerated, as only one patient (with a level of 24.8mg/l) had relatively mild side effects, supporting the proposed upper limit of the reference range (Cawello, 2015; Novy et al., 2013; Patsalos, 2013). The rare occurrence of cardiac arrest after exposition to LCM high doses (Chua-Tuan et al., 2015) also illustrates the risk of exposing patients to unnecessarily high doses.

4.2. Strength and limitations

This study has some limitations. First, the retrospective identification of patients can lead to inclusion and information bias. However, we collected serum levels for the majority of patients treated with intravenous LCM during the study period, and clinical variables were comparable among included and excluded patients. Second, the possible unequal distribution of outcome predictors between responders and non-responders may have masked an effect of LCM loading dose. We applied a correction for three potentially confounding variables (STESS, potentially fatal aetiology, position of LCM in treatment), using multivariable analysis, one factor at a time.). However, the power of this analysis is strongly limited by the sample size of 40 patients that do not allow to include other potentially confounding variable and make it difficult to formally exclude any bias. A large randomised prospective clinical trial is needed to overcome these points. Third, the SE response definition (last drug added that terminates SE) is admittedly simplistic and does not take into account potential synergistic effects or the natural evolution of the SE episode. This represents however a practical clinical criterion. Fourth, the comparison between our patients and those treated with LCM but without available serum showed a trend towards more males patients, more potentially fatal aetiologies and more mortality in the non-included patients. This was not statistically significant but, as the number of excluded patients is relatively small (20), differences cannot be firmly excluded.

Conversely, the prospective collection of pertinent clinical data in the registries represents a strength for the internal validity of the study. We assumed that trough serum levels were a

reliable surrogate of the overall exposition, which might also be a simplification. Trough levels represent however a readily available measure in clinical practice and are easily interpretable for clinicians.

4.3. Conclusion

In conclusion, in adults with SE a loading dose of at least 9mg/kg is associated with a LCM serum level within the reference range for chronic epilepsy, but without correlation with the clinical response in SE in our cohort. These data question the benefit of increasing further LCM loading doses in SE. Prospective studies are needed to evaluate the benefit of increasing the LCM loading dose in SE. .

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Author's contribution:

MP: study concept and design, acquisition of data, analysis and interpretation, redaction of the manuscript.
PA: acquisition of data, critical revision of the manuscript for important intellectual content.
VA: acquisition of data, critical revision of the manuscript for important intellectual content
CS: acquisition of data, critical revision of the manuscript for important intellectual content.
LAD: lacosamide levels measurements, acquisition of data, critical revision of the manuscript for important intellectual content
AOR: study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision.
JN: study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision.

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Figure captions

Figure 1:

Distribution of lacosamide intravenous loading dose according to the resulting serum level, dichotomised according to the reference range (>10mg/l or below)(p=0.002, U test).

Figure 2:

Comparison of lacosamide serum level between responders and non-responders (p=0.24).

Table 1

Characteristics	Responders (n=16)	Non responders (n=24)	p-value	Test used
Age – years, median (range)	67 (34-88)	69 (34-85)	0.85	U
Gender – males, n (%)	7 (44%)	12 (50%)	0.70	χ 2
Potentially fatal cause, n (%)	9 (46%)	15 (63%)	0.69	χ 2
Favourable STESS of < 3/6, n (%)	9 (56%)	3 (13%)	0.005	Fisher
SE duration before LCM – hours. Median (range)	34 (3-291)	25 (2-150)	0.7	U
Time from LCM loading to SE cessation – hours, Median (range)	14 (0-49)	90 (5-879)	<0.001	U
Mortality (at hospital discharge), n (%)	0 (0%)	5 (21%)	0.07	Fisher
Total number of AEDs used, Median (range)	3 (2-4)	5 (3-9)	<0.001	U
Position of LCM in the treatment sequence, Median (range)	3 (2-4)	3 (1-6)	0.58	U
LCM Loading dose – mg, Median (range)	600 (200-800)	600 (100-800)	0.79	U
Loading dose / body weight - mg/kg, Median (range)	7.7 (2.2-16)	7.5 (1.3-13.3)	0.97	U
LCM serum level – mg/l, Median (range)	10.4 (2.4-24.8)	9.5 (3.5-16.9)	0.36	U
Time between LCM loading dose and serum level – h, Median (range)	14.75 (6.25-34.75)	17.4 (11.75-26.5)	0.31	U
Time between last LCM dose and serum level – h, Median (range)	10 (6-14.5)	11.75 (6-16.5)	0.14	U

Table 1: Characteristics of the patients and SE episodes according to response to LCM.