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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 (10–20 mg/l) were associated with loading doses of > 9 mg/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. Prospective studies are needed to evaluate the benefit of increasing the LCM loading dose 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 400 mg daily for maintenance treatment; the proposed reference serum interval lies between 10 and 20 mg/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). Ideal loading doses remain however uncertain.

Boluses of 200–400 mg are usually administered in SE (Höfler and Trinka, 2013), and a small prospective study suggested that 400 mg could possibly prove more efficacious than 200 mg (Legros et al., 2014). It was recently observed that loading doses of 8 mg/kg (approximately 550 mg for a 70 kg patient) were needed to reach a serum level within the reference interval (Ramsay et al., 2015) and that doses of more than 10–12 mg/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.

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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; Sutter et al., 2013b), 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 h after the loading dose were excluded to allow analysis of uniform trough serum levels. A reference of 10–20 mg/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 h 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 (3th 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 600 mg (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 mg/kg).

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 h (range 6.25–34.75 h).

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) (Fig. 1). A loading dose of 9 mg/kg or more was associated with levels within the reference range ($p = 0.003$, $\chi 2$). 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.