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ORIGINAL ARTICLE

Status epilepticus prognosis following levetiracetam administration: Analysis of loading doses

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Abstract

Background and purpose: Recommended loading doses of levetiracetam (LEV) for status epilepticus (SE) treatment have increased over time. However, this was not evidence-based, and the benefit of the increase remains unclear. The effect of different LEV loading doses on SE prognosis was explored.

Methods: This is a retrospective analysis of an SE adult registry (January 2016–December 2021), including patients receiving LEV as a second-line SE treatment. Patients were stratified according to LEV loading doses (threshold 35 mg/kg). Main outcomes were global mortality, LEV use as last SE treatment, and return to baseline conditions at discharge, exploring LEV as a dichotomized or continuous dose.

Results: Among 202 patients, 44 received LEV at ≥35 mg/kg and 158 below it. Global mortality, adjusted for SE severity and potentially fatal aetiology, was more frequent in the high LEV dose group (27.2% vs. 17.1%, odds ratio 3.14, 95% confidence interval 1.23–8.06; $p = 0.017$), whilst LEV prescription as last treatment and return to baseline conditions were comparable. Considering continuous LEV dosages or mortality in ongoing SE, however, no outcome reached statistical significance.

Conclusions: Lower LEV loading doses do not seem to correlate with worse clinical outcome, challenging current guidelines. Further studies, ideally prospective, are needed on this topic.

KEYWORDS
mortality, outcome, second-line, treatment

INTRODUCTION

Status epilepticus (SE) is a condition characterized by prolonged or repeated epileptic seizures without full recovery in between [1]. It can have long-term consequences, including neuronal injury and alteration of neuronal networks, depending on the type and duration of seizures [2]. This neurological emergency occurs in around 20/100,000 people per year [3, 4], with significant morbidity and mortality [5]. Prognosis is influenced by various factors, mostly related to the underlying biological background (such as age, medical comorbidities, previous epilepsy diagnosis) and characteristics of the SE event (e.g., aetiology, level of consciousness, seizure type and duration) [5].

While a rapid and effective treatment is advocated to prevent potential cerebral and systemic damage, or death [6], the recommended treatment plan is classically subdivided into three consecutive lines, consisting of the intravenous administration of benzodiazepines (first-line), anti-seizure medications (ASMs) (second-line therapy) and general anaesthetics (third-line) [7, 8].

Notably, a recent randomized trial on adults and children did not disclose any difference favouring one of the three ASMs frequently

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used as second-line (levetiracetam [LEV], valproate [VPA] or phosphenytoin) [9]. In that study, the LEV loading dose was prescribed at 60 mg/kg, representing roughly double the European recommendations of 2010 [7]. To our knowledge, this dose is not based on any solid evidence; additionally, a previous study did not find any clear relationship between SE treatment success and LEV residual serum levels following loading [10]. In this context, it appears clinically relevant to explore the effect of different LEV loading doses on the prognosis of SE patients. Our SE registry, which reflects the change over time of the recommended LEV loading in our in-house SE treatment protocol, was therefore analysed, hypothesizing that higher LEV loading doses would allow a better SE control and favourable clinical outcome.

METHODS

Study population

In this retrospective observational study, our institutional SE registry including adults (>18 years old) was screened, identifying those receiving LEV as a second-line treatment between January 2016 and December 2021 (6 years). This period includes the change of practice regarding LEV loading dose (20–30 mg/kg until the end of 2019 [7], 40–60 mg/kg since then, following the aforementioned trial [9]). SE was defined in the registry as a generalized tonic–clonic seizure lasting >5 min, focal or absence episodes lasting >10 min, or consecutive seizures without complete recovery between the episodes over the same time frames [1, 10]. Non-convulsive episodes needed an electroencephalogram (EEG) for diagnostic confirmation. Episodes after cardiac arrest were excluded because of important prognostic differences. SE resolution was determined clinically and confirmed by EEG within 24 h. The registry has been approved by our ethics commission (CER-VD, project-ID 2022-00541); consent was waived (observational analysis), but patients refusing general consent to research were excluded from analysis according to Swiss law. The relationships between clinical variables of interest and outcomes were investigated after stratifying patients into two groups according to the LEV loading dose, using a discriminant threshold of 35 mg/kg (lying between the recommendations of 20–30 and 40–60 mg/kg), and on the whole cohort.

Variables and outcomes

Registry data include demographics, body weight, time of SE start and end, consciousness before treatment, worst seizure type (classified, in increasing order of severity, as: focal aware, absence or generalized myoclonic, focal unaware, generalized convulsive, and non-convulsive in coma) and history of previous seizures. Consciousness is categorized as alert, somnolent/confused, stuporous/comatose. Aetiologies are considered as 'potentially fatal' if probably leading to death independently of SE (namely, acute large vessel ischaemic stroke, acute cerebral haemorrhage, acute central nervous system infection, malignant brain tumour or metastases, acquired immune deficiency syndrome with central nervous system complications, chronic renal insufficiency requiring dialysis, systemic vasculitis, metabolic disturbance or acute intoxication sufficient to cause coma in the absence of SE, eclampsia). Conversely, ASM withdrawal and remote or progressive conditions (previous trauma, stroke, central nervous system infection, dementia, multiple sclerosis, low-grade glioma or meningioma) are not considered potentially fatal [1, 11]. The Status Epilepticus Severity Score (STESS), a validated tool [12] assessing the gravity of SE episodes based on age, consciousness before treatment, seizure type and previous seizures, is prospectively calculated on admission. The newly described ACD score (based on age, consciousness impairment and SE duration) was also retrospectively calculated [13]. Medications (previous ASM; type, timing, loading doses of compounds administered to treat the index episodes, and need for mechanical intubation for SE treatment or airways protection) are prospectively entered. At patient's discharge from acute hospitalization, mortality (including if patients died in ongoing SE and reason for death) and return to baseline clinical conditions are prospectively recorded.

An 'adequate initial SE treatment' was defined based on current guidelines (lorazepam 0.1 mg/kg, midazolam 0.15 mg/kg, clonazepam 0.015 mg/kg) [7, 8, 14] if at least half the recommended benzodiazepine dose was administered. The primary outcome was in-hospital global mortality, calculated on patients (in the case of recurrent episodes, the last was considered). As secondary outcomes, mortality in ongoing SE, LEV use as a last treatment, and the return to baseline clinical conditions at discharge were considered.

Statistical analysis

Calculations were performed using Stata version 16 and SPSS version 27.0 (IBM Corp.). For univariable analyses, Student's *t*, chi-squared, two-sided Fisher's exact and Mann–Whitney *U* tests, or Spearman's correlations, were applied as needed. Analyses on the outcomes were adjusted using multivariable logistic regressions for potentially confounding variables having $p < 0.1$ in univariable analyses for global mortality, with particular attention for STESS and potentially fatal aetiology [15].

RESULTS

Demographics and clinical variables

A total of 887 SE episodes were registered over the considered time frame, of which 228 received a loading dose of LEV as a second-line treatment; 15 patients declined the general consent for research and were excluded. This left 213 episodes occurring in 202 patients (11 patients were involved twice). In 168 episodes (158 patients) LEV was given below 35 mg/kg (mean 24.7 ± 7.3 mg/kg), whilst in 45 (44

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patients) it was given at or above this threshold (mean 53.8 ± 11.5 mg/kg). Detailed clinical variables and the differences between the LEV loading dose groups are shown in Table 1. Demographics and clinical variables were globally comparable across the groups, including STESS and ACD scores, pre-existing LEV use, time to first SE treatment, time to LEV, and 'adequate initial SE treatment' (at least half of the recommended benzodiazepines loading dose). Median SE duration was non-significantly longer for the low dose group ($p = 0.061$, Mann–Whitney *U*). Patients who died had significantly longer SE durations (36 h [interquartile range 10–144] vs. 11.5 h [interquartile range 2.75–48] for survivors; $p = 0.004$; Mann–Whitney *U*). The need for intubation was not different across the groups, regardless of the reasons.

Table 2 illustrates in the left columns the correlation between relevant clinical parameters and LEV loading doses, treated as a continuous variable; SE duration was the only statistically significant item (higher doses, shorter duration). The right columns show univariate logistic regressions towards global mortality; potentially fatal aetiology and STESS score were significantly related to it.

Outcomes

Table 3 summarizes multivariable logistic regressions for the outcomes using LEV loading doses dichotomized at 35 mg/kg. After adjusting for STESS and potentially fatal aetiology, global mortality (the

TABLE 1 Detailed clinical variables according to the levetiracetam loading dose

Clinical variables	<35 mg/kg (168 episodes)	≥35 mg/kg (45 episodes)	Test	*p*
Sex				
Female	73 (43.4%)	19 (42.2%)	χ^2	0.882
Age (years, mean ± SD)	64.4 (±17.5)	66.4 (±17.4)	*t*	0.483
Consciousness before SE treatment				
Alert	20 (11.9%)	5 (11.1%)	χ^2	0.699
Somnolent or confused	52 (31.0%)	12 (26.7%)		
Stuporous or comatose	96 (57.1%)	28 (62.2%)		
Worst seizure type				
Focal aware	29 (17.2%)	8 (18.2%)	Fisher	0.986
Absence or generalized myoclonic	3 (1.8%)	0 (0%)		
Focal unaware	43 (25.6%)	11 (25.0%)		
Generalized convulsive	73 (43.4%)	21 (47.7%)		
Non convulsive in coma	20 (11.9%)	4 (9.1%)		
Previous seizures	55 (32.7%)	12 (27.3%)	χ^2	0.488
Potentially fatal aetiology	93 (55.4%)	21 (47.7%)	χ^2	0.366
STESS score (median, IQR)	3 (2–4)	3 (2–4)	*U*	0.994
ACD score (median, IQR)	8 (6–10)	8 (6–9)	*U*	0.531
LEV prescribed before SE start	23 (13.7%)	7 (15.6%)	χ^2	0.749
Time to first SE treatment (min, median, IQR)	88 (30–359)	157 (30–360)	*U*	0.434
Time to LEV (min, median, IQR)	150 (60–480)	195 (95–375)	*U*	0.278
LEV loading dose (mg/kg, mean ± SD)	24.7 (±7.3)	53.8 (7.5)	*t*	**<0.001**
Adequate initial SE treatment (see text)	97 (58.8%)	28 (62.2%)	χ^2	0.677
SE duration (h, median, IQR)	18 (3.5–72)	7.25 (2.4–36)	*U*	0.061
Need of intubation				
No	109 (65.3%)	29 (64.4%)	Fisher	0.405
Yes, for SE treatment	29 (17.4%)	11 (24.4%)		
Yes, for airways protection	29 (17.4%)	5 (11.1%)		

Note: Bold values are significant.

Abbreviations: ACD score, score containing age, consciousness, duration of the episode; IQR, interquartile range; LEV, levetiracetam; SD, standard deviation; SE, status epilepticus; STESS, Status Epilepticus Severity Score (age, seizure type, consciousness, previous seizures).

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TABLE 2 Univariable correlations between the main clinical variables and outcomes towards LEV loading dose (as continuous variable), in the whole studied cohort (213 episodes)

	Relationship towards LEV dose (213 episodes)	Test	*p*	OR (95% CI) towards global mortality (202 patients)	*p*
Potentially fatal aetiology	$Z=0.283$	*U*	0.778	5.17 (2.16–12.40)	**<0.001**
STESS score	Rho = 0.092	Spearman	0.179	1.96 (1.49–2.57)	**<0.001**
Time to first SE treatment	Rho = 0.103	Spearman	0.145	1.000 (0.999–1.000)	0.659
Time to LEV treatment	Rho = 0.076	Spearman	0.272	1.000 (0.999–1.000)	0.678
Adequate initial treatment (see text)	$Z=-0.899$	*U*	0.360	0.726 (0.357–1.477)	0.376
SE duration	Rho = −0.152	Spearman	0.032	1.000 (0.999–1.001)	0.125

Note: Bold values are significant.

Abbreviations: CI, confidence interval; LEV, levetiracetam; OR, odds ratio; SE, status epilepticus; STESS, Status Epilepticus Severity Score (age, seizure type, consciousness, previous seizures).

TABLE 3 Outcome variables according to levetiracetam loading doses (dichotomized at 35 mg/kg)

	<35 mg/kg (168 episodes, 158 patients)	≥35 mg/kg (45 episodes, 44 patients)	Adjusted OR[a] (95% CI)	*p*
LEV as last treatment (on 213 episodes)	70 (39.1%)	21 (46.7%)	1.13 (0.69–2.70)	0.378
Return to baseline conditions at discharge (on 213 episodes)	60 (35.7%)	11 (24.4%)	0.53 (0.24–1.20)	0.129
Global mortality (on 202 patients)	27/158 (17.1%)	12/44 (27.2%)	3.14 (1.23–8.06)	**0.017**
Mortality in ongoing SE (on 202 patients)	9/158 (5.4%)	2/44 (4.6%)	0.92 (0.18–4.56)[b]	0.921

Note: Bold values are significant.

Abbreviations: CI, confidence interval; LEV, levetiracetam; OR, odds ratio; SE, status epilepticus.

[a]Adjusted for Status Epilepticus Severity Score (STESS), potential fatal aetiology.

[b]Exploratory analysis (given the limited number of patients with the outcome of interest).

TABLE 4 Analyses of the relationship between the outcomes and LEV loading dose (considered as continuous variable)

	Univariable OR (95% CI)	*p*	Adjusted OR[a]	*p*
LEV as last treatment (on 213 episodes)	1.02 (1.00–1.04)	0.055	1.02 (1.00–1.04)	0.077
Return to baseline conditions at discharge (on 213 episodes)	0.99 (0.97–1.01)	0.451	0.99 (0.97–1.01)	0.637
Global mortality (39 of 202 patients)	1.01 (0.98–1.03)	0.665	1.01 (0.98–1.04)	0.372
Mortality in ongoing SE (11 of 202 patients)	0.99 (0.95–1.04)	0.661	0.99 (0.94–1.04)[b]	0.705

Abbreviations: CI, confidence interval; LEV, levetiracetam; OR, odds ratio; SE, status epilepticus.

[a]Adjusted for Status Epilepticus Severity Score (STESS), potential fatal aetiology.

[b]Exploratory analysis (given the limited number of patients with the outcome of interest).

primary outcome) occurred more frequently in the high LEV dose group. Of note, 9/27 (33%) in the low dose group versus 2/12 (17%) patients in the high dose group died in ongoing SE ($p=0.446$, Fisher); the others died mostly due to underlying conditions including SE aetiology (Table S1 gives details of death causes, without any statistical distribution difference across LEV groups). LEV prescription as last SE treatment and return to baseline condition showed no statistical difference. Table 4 summarizes multivariable analyses using LEV as a continuous variable: whilst impacts on mortality and return to baseline condition are far from significance, LEV as last treatment showed a non-significant association towards higher loading doses.

DISCUSSION

In this retrospective observational study, contrary to our hypothesis, it was found that patients receiving lower LEV loading doses for SE treatment did not have worse clinical outcome.

Over the last 10 years, there has been a trend to increasing doses in second-line SE treatment, particularly regarding LEV. Indeed, the 2010 European guidelines on the management of SE in adults recommended boluses of 25–45 mg/kg VPA and 1000–3000 mg LEV (considering an average of 80 kg for an adult, this corresponds to 12.5–37.5 mg/kg) [7]. Six years later, the American recommendations

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foresaw 40 mg/kg VPA for a maximal dose of 3000 mg and 60 mg/kg LEV for a maximal dose of 4500 mg [7, 8]; this was applied in the ESETT randomized trial [9].

Increasing loading doses of second-line ASM were not convincingly shown to improve SE outcome. LEV residual blood levels were not related to SE control, although a loading of 30 mg/kg seemed sufficient to reach an adequate exposure [10]; this supports a recent retrospective analysis of the ESETT trial, which suggested that the doses (capped at 75 kg) probably resulted in higher concentrations than those needed for efficacy [16]. Lacosamide, an alternative second-line treatment, also did not show a clear relationship between its post-loading blood levels and efficacy [17]. In addition, a recent analysis found that VPA loading (and corresponding blood levels) did not correlate with SE control and mortality. Conversely, brivaracetam, which is used as a second-line option, was shown in a small study to correlate with better clinical responses in SE if loaded at higher dose (at around 2 mg/kg) [18]. To unify these findings, it seems reasonable to postulate ceiling effects for LEV (at around 30 mg/kg), VPA (20–30 mg/kg) and lacosamide (4–5 mg/kg), and at around 2 mg/kg for brivaracetam.

Multivariable analyses, adjusted for the most important mortality predictors (STESS and potentially fatal aetiology), differed depending on whether LEV loading doses were considered as discrete or continuous variables. Dichotomizing at 35 mg/kg showed a higher global in-hospital mortality in the high dose group, whilst the proportion of return to baseline conditions and LEV as last SE treatment (used as a surrogate of SE control) were comparable. Considering continuous values, higher LEV was conversely not related to mortality (and, again, return to baseline), but showed a non-significant tendency to be more frequently associated with LEV as last treatment; also, in univariable exploration it correlated with shorter SE duration. Of note, when restricting analyses of mortality to patients dying in ongoing SE, the relationship between LEV doses and outcome was not significant.

These divergent findings on mortality call to caution in driving direct conclusions, especially regarding the categorized LEV dosage (whose threshold, however, practically corresponds to the evolution of treatment recommendations); in any case, no signal was found that increased LEV loading doses correlate with better clinical outcome. The association of shorter SE duration with higher dosage, if formally confirmed in a larger cohort, could suggest that higher LEV loading may be related to faster SE control. This seems at first glance to be in contrast with previous studies, where longer SE duration correlated with mortality [13, 19, 20]. In our cohort, patients who died had indeed longer SE durations, and those receiving higher LEV doses tended non-significantly to die more often after successful SE control (i.e., probably owing to underlying conditions, including the SE cause). In an intensive care unit environment, SE aetiology has been shown to exert a greater influence on outcome than its duration [21]; in view of the highly complex relationship between SE and outcome, as nicely illustrated in a recent work [19], these interactions deserve further investigations.

Globally, these findings reinforce the hypothesis that SE treatment seems to probably exert less impact on SE prognosis compared to the underlying biological background [1, 5, 15]. To our knowledge, this is the first study analysing the relationship between a wide range of LEV loading doses, up to 60 mg/kg, and SE prognosis. While it relies on a prospectively acquired institutional registry filled by two authors (J.N., A.O.R.), allowing a good internal validity, our analysis should be interpreted in the light of several limitations. It is based on a single centre recruiting adults, although mortality seems to be in line with other similar cohorts (19% in an Italian study [22] and, again, 19% in a multicentre German assessment [23]). The sample size was relatively limited, especially for the higher dose group and patients dying in ongoing SE. Analyses were retrospective and treatment allocation was not randomized. Laboratory parameters (such as inflammatory proteins or renal function) are not reported in the registry [5, 21]. Finally, confounding factors that remained undetected cannot be excluded.

In conclusion, in adults with SE who received LEV as a second-line treatment, lower LEV loading doses do not seem to correlate with worse clinical outcome (mortality, chances to return to clinical baseline conditions). The finding of higher in-hospital global mortality in patients receiving more than 35 mg/kg might challenge current clinical practice, and, in line with findings on other ASMs used for SE treatment, should represent a rationale for adequately powered phase II trials investigating SE responses to increasing ASM loading doses in terms of clinical outcome (mortality, new handicap) and SE control.

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CONFLICT OF INTEREST STATEMENT

The authors report there are no competing interests to declare.

DATA AVAILABILITY STATEMENT

Anonymized original data will be provided upon request from qualified researchers.

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