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Circulating concentrations of levetiracetam in patients treated for status epilepticus and assocation with therapeutic response

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Abstract word count: 248
Manuscript word count:
The manuscript includes.

Keywords:

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Abstract

Introduction: Intravenous levetiracetam (LEV) is broadly used in the treatment of status epilepticus (SE). A loading dose is usually infused, aiming to reach quickly the range of plasma concentrations considered as therapeutic (12-46 mg/L). We evaluated the potential therapeutic interest of LEV plasma concentrations in patients with SE by comparing responders and non-responders.

Material and Methods: Retrospective analysis of a SE registry, including patients since 2015 with at least one available LEV plasma level measured less than 36 hours after loading. A Bayesian maximum likelihood approach based on a population pharmacokinetic model was used to estimate LEV exposure parameters. We compared plasma levels and pharmacokinetics parameter estimates between responders and non-responders. Therapeutic response was defined as SE cessation within 24 hours following LEV introduction.

Results: Between February 2015 and April 2016, we included 29 patients (45 plasma levels). Variability was salient in LEV dosages administered and monitoring practice. There were no difference in median plasma concentrations (19.5 versus 21.5 mg/l; p=0.71), median estimated LEV exposure (25.8 versus 37.0 mg/l, p=0.58), peak (30.4 versus 41.5 mg/l, p=0.36) or residual levels after loading dose (14.4 versus 20.5 mg/l, p=0.07) between responders and non-responders.

Conclusion: LEV exposure does not seem to significantly differ between responders and non-responders. Loading doses of 30 mg/kg seem however appropriate to quickly reach the target exposure level. Variability in LEV dosing and monitoring precludes firm conclusions about concentration-response associations, which deserve further systematic investigation.

Introduction

Status epilepticus (SE) is a neurologic emergency (Trinka et al., 2015) that can lead to serious morbidity and mortality, especially when prolonged (Betjemann and Lowenstein, 2015) (https://www.ncbi.nlm.nih.gov/pubmed/28681418). Strong evidences support the use of benzodiazepines as first line treatment; the second line is based on weaker evidence, and typically consists of non-sedative antiepileptic drugs (AED) given intravenously. Three AEDs have been commonly prescribed since several years: phenytoin, valproate and levetiracetam (LEV) (Brophy et al., 2012; Glauser et al., 2016; Meierkord et al., 2010), while lacosamide is also increasingly used.

LEV is a broad-spectrum AED available intravenously since 2007 in Switzerland, targeting the synaptic vesicle protein 2 (SV2a) (Deshpande and DeLorenzo, 2014). It is eliminated mostly through the renal route and has a low potential for drug to drug interaction, and induced sedation is mild (Trinka and Dobesberger, 2009); it is therefore one of the most widely prescribed AED in SE (Brigo et al., 2016) and its use seems to be increasing (https://link.springer.com/article/10.1007%2Fs40263-017-0424-1).

The objective regarding the use of a loading dose is to reach without delay the reference plasma level interval, which for LEV is reported between 12 and 46 mg/l in chronic epilepsy patients (Patsalos et al., 2008). The ideal LEV loading dose is not established: in consecutive guidelines, there is a trend toward increasing doses (**table 1**). Maintenance LEV dosage should then keep circulating concentrations between those boundaries. In our centre, loading dose of 30 mg/kg is recommended. Estimated drug exposure through LEV plasma concentrations may help to validate a rational loading dose able to produce the desired exposure.

Our study aimed at evaluating the current use of LEV in SE, and at clarifying the potential therapeutic interest of LEV plasma concentrations in acute SE management. In particular, we looked for an association between plasma levels and achievement of therapeutic response.

Materials and Methods

This is a retrospective analysis of our previously described prospective SE registry (Novy et al., 2010), which is approved by our institutional review board and includes all consecutive adult patients with SE treated at the CHUV (Lausanne University Hospital). Inclusion is performed by two epileptologists (JN and AOR) based on clinical evaluation and EEG (the

latter being mandatory for nonconvulsive episodes). SE is defined as a single seizure lasting more than 5 minutes, or shorter consecutives seizures without complete recovery between the episodes. Episodes occurring in patients younger than 16 years old or post-cardiac arrest are excluded because of important differences in prognosis. Resolution of SE was determined as the moment of seizure cessation, as demonstrated by clinical examination and subsequently confirmed by EEG documentation, usually obtained within 24 hours.

For every episode, detailed patients demographics and body weight were prospectively collected, together with SE duration and clinical characteristics, including presence of a potentially fatal aetiology, as defined previously (Rossetti et al., 2006). The Status Epilepticus Severity Score (STESS), a validated composite prognosis score based on four items (age, consciousness before treatment, worst seizure type and previous history of seizure (Rossetti et al., 2008), was calculated on admission. The exact sequences of administration of LEV and other AEDs, with loading and maintenance doses including timing of injections, were also prospectively recorded. The loading dose was defined as a single or serial LEV administrations given at close intervals (less than 4 hours) with the aim of reaching therapeutic concentrations. For the purpose of this study, therapeutic response to LEV was assumed if LEV was the last AED introduced in the 24 hours before SE resolution. The interval between LEV loading and response (either end of SE for responders, or introduction of another AED for non-responders) was defined as the observation period.

We screened all patients having received LEV for SE between February 2015 (when this test became available in our laboratory) and April 2016, including those with LEV plasma levels collected during 36 hours after the loading dose, defined as the first dose of the initiated treatment. Further LEV plasma levels were collected if they were sampled within 7 days following SE onset, and used to adjust an individual LEV pharmacokinetic model. All data concerning dosage regimen, time of blood sampling, serum creatinine, ammonium and comedications was retrospectively collected. Levels were determined using ultra-performance liquid chromatography with tandem mass spectrometry (Decosterd et al., 2015). In case of recurrent SE episodes in a single patient, only the first episode was included in the analysis. To evaluate a potential inclusion bias, we compared this study cohort with the other patients concomitantly treated with LEV in our centre (also prospectively included in the registry), in whom no LEV plasma levels were available.

LEV plasma concentration values were interpreted based on a population pharmacokinetic model (Pigeolet et al., 2008), describing LEV disposition by a one-compartment open model with first order elimination and additive residual error. According to this model, LEV apparent clearance is affected by various covariates retrieved in each patient (body weight, gender, creatinine, clearance and concomitant intake of enzyme inducers or inhibitors). Similarly, LEV distribution volume depends on bodyweight, disease, and comedication with valproic acid. Using this model, a Bayesaian maximum-likelihood approach was applied to the available sparse samples, and a posteriori parameters were determined for each patient and used to estimate individual LEV exposure. The pharmacokinetic analysis was performed using the NONMEM program (version 7.3), running with Pirana (2.9.3) and PSN-toolkit (4.2)(Keizer et al., 2011).

LEV exposure was assessed with two parameters: plasma level measured within 36 hours (obtained from the laboratoy files) and mean concentration during the exposure period (derived from the individualized pharmacokinetic model as the area under concentration curve divided by the duration of the observation period). In addition, peak and trough LEV concentrations were extrapolated based on the same model, and defined as the maximal and minimal concentrations reached between the loading and the first maintenance dose.

For statistical analysis, patients were divided according to their therapeutic response to LEV. We compared LEV exposure between both groups using a Mann-Whitney U-test. Both groups were further compared for other available clinical characteristics using Chi-Square, Fisher, Mann-Whitney U and Spearman tests, as required. Secondarily, data were adjusted (sequentially using one corrector each time given the sample size) for predictors of outcome, such as position of LEV in the treatment, STESS, and potentially fatal SE aetiology (Novy et al., 2010; Sutter et al., 2013), in a binary logistic regression. Calculations were done with *SPSS version* 23.0 (IBM corp., Armonk, NY).

Results

Between February 2015 and April 2016, 81 patients with SE were treated with at least a loading dose of LEV in our centre. We identified 29 (36%) patients with available plasma levels, among whom 23 (79%) were newly treated by levetiracetam. These 29 patients are the object of this analysis.

As an internal validity assessment, the 29 included patients were comparable to the 52 other patients receiving LEV during the same period, but without plasma level measurement, regarding therapeutic response (34% versus 29%; p=0.6, χ 2), potentially fatal etiologies (57% versus 62%, p=0.7, χ 2), mortality at discharge (10% versus 20%, p=0.4, Fisher test), favourable STESS of <3 (24% versus 21%, p=0.8, χ 2), total number of AEDs used (median: 3 versus 3, p=0.96, U test) and position of LEV within the treatment sequence (median: 2th versus 2th, p=0.2, U test).

Among the included patients, a therapeutic response to LEV was observed in 10 (35%). Detailed demographics, clinical and treatment characteristics comparing responders and non-responders are given in **table 2**. There was no significant difference between both groups. LEV loading doses varied between 1000 and 3000 mg, with a median of 2000 mg, representing 27.8 mg/kg body weight with a range of 17.2 to 38.5 mg/kg. This loading dose tended to be somewhat lower in responders, while non-responders received a higher cumulated LEV doses essentially because of the SE longer duration. We did not record any side effects directly related to LEV treatment.

Overall, 46 plasma levels were available, among which 29 were collected within 36 hours. The majority (82%) were above the lower reference limit of 12 mg/l. Plasma levels were measured most frequently after one loading dose plus one maintenance dose (n=13; 45%). Only 2 patients (8%) had a plasma level obtained just after a loading dose. According to usual recommendations, pharmacokinetic steady state is reached only after at least 4 identical doses, this constellation corresponded only to 11 plasma levels (25%) in 9 patients (31%). Median time between loading dose and the first considered plasma level was 17 hours (range 7-37h). Finally, the time between last dose and blood sampling appeared highly variable, with a median of 8.5 h (range 0.9-15.3 h).

The measured plasma levels did not correlate with the corresponding loading doses (p=0.85, Spearman) or loading doses adjusted to bodyweight (p=0.12, Spearman) (**figure 1**), even when considering only plasma levels obtained before 36 hours (p=0.81 for loading dose; p=0.96 for loading dose related to body weight, Spearman). Conversely, mean plasma levels derived from the pharmacokinetic model during the observation presented the expected, correlation with LEV loading doses (p<0.001, Spearman). Collected and calculated plasma levels are displayed in **table 3**.

No difference in LEV exposure was observed between responders and non-responders, for both the plasma levels measured before 36 hours (p=0.71, U test) and the calculated mean, peak and trough plasma levels (p=0.61, 0.36 and 0.37 respectively, U test). There was a trend toward higher plasma concentration at the time of response determination in non-responders (25.4 versus 36.0, p=0.07, U test).

Adjusting the measured plasma levels after loading dose for LEV position in the treatment sequence (odd-ratio OR: 0.98; 95% confidence interval CI: 0.91-1.07; p=0.73), potentially fatal etiology (OR: 1.01; CI: 0.93-1.009; p=0.9), or STESS (OR: 1.004; CI: 0.93.1.08; p=0.92) did not reveal any difference. Similarly, calculated mean LEV plasma levels did not show any association with clinical response after adjustment for position of LEV in the treatment (OR: 0.93; CI: 0.85-1.02; p=0.14); fatal etiology (OR: 0.97; CI: 0.90-1.04; p=0.41), and STESS (OR: 0.98; CI: 0.92-1.05; p=0.53).

To assess the ideal loading dose, a peak level of 40 mg/L was targeted, considering the upper limit of the reference range. According to model-based extrapolations of peak concentrations, a loading dose of 30 mg/kg seemed optimal to reach this target in most patients (figure 3). Maintenance doses can be started 12h later, in line with the biological half-life of LEV (estimated between 7.7 and 12.4 h in our patients). The maintenance dosage should then be adapted based on renal function.

Discussion

The lack of correlation observed between measured plasma levels and loading doses seems due to highly variable sampling times after loading injection. The rather short LEV plasma half-life (suggested to be even shorter in critical setting, Spencer) explains the marked confounding effect of this variability. Measuring LEV plasma levels in this clinical setting seems thus of little value beyond merely ascertaining that the patient has received the drug. LEV exposure would be more properly assessed through a standardised protocol with consistent intervals between the administration of loadings doses and the collection of blood samples.

To overcome the limitations of our direct plasma measurements, we further characterised LEV exposure in the patients using a pharmacokinetic model previously validated in Caucasian subjects (Pigeolet et al., 2008). This calculation integrated influential covariables and estimated maximum likelihood LEV exposure in each patient, assumed to represent a more robust indicator of LEV activity (Spencer et al., 2011). The number of patients and blood levels precluded the elaboration of a proper population model. This approach adequately correlated the loading dose with the estimated peak plasma level, but failed to identify any difference in LEV exposure between responders and non-responders. Several considerations might explain this finding.

Firstly, the spread of LEV exposure levels was relatively limited in our study, thus precluding the observation of markedly underdosed or overdosed patients. Secondly, the reference therapeutic plasma interval of 12-46 mg/l has been established in patients having chronic epilepsy, but not in SE, which might necessitate different and possibly higher levels, as suggested e.g. for topiramate (Wyllie et al., 2011). Thirdly, blood and brain compartments display different pharmacokinetic properties regarding LEV: animal studies (Doheny et al., 1999; Nicolas et al., 2016) showed indeed a mismatch between plasma and central nervous system levels. LEV elimination from the central compartment is probably slower than from circulation, thus explaining LEV sustained efficacy when given twice daily in spite of the relatively short half-life (Perucca and Johannessen, 2003). Plasma levels may thus be of limited help to predict the availability of treatment at its biological target. Fourthly, the relationship between blood or brain exposure and therapeutic efficacy might display important between-patient pharmacodynamic variability: a similar observation was done for lacosamide in the same clinical setting (Perrenoud et al., 2017). Making a parallel with

chronic epilepsy in an outpatient setting, most of the medication effect in responders is usually obtained at low dosage, and increasing doses seem to bring little additional benefit in terms of remission (D'Anto et al., 2017; Poolos et al., 2017)

Our response rate to LEV was 34%, lower than previous studies with similar dosages that reported rates of 68.5% in 204 episodes (Yasiry and Shorvon, 2014), or 65.4% in 156 episodes (Trinka and Dobesberger, 2009). Direct comparisons are however difficult, because the definition of clinical response was not uniform across those studies and most of them, as ours, had a retrospective design making them prone to inclusion bias. Our response rate appears congruent with a previous study in our centre reporting a response rate of 51.7% in 58 episodes (Alvarez et al., 2011). In that study, LEV was given as a second line treatment, which is also the case for 22 (76%) of our patients, and the definition of response did not include the 24h criterion, thus potentially leading to a higher rate.

Our study has limitations. Firstly, our response definition represents a simplification of the complex factors determining SE cessation, and does not consider the potential effects of agents previously introduced. It represents however a pragmatic and objective endpoint from a clinical view (Redecker et al., 2017). Secondly, the retrospective design and relatively limited number of patients prevents drawing any firm conclusions: e.g. the "ideal" loading dose of LEV found to be 30 mg/kg deserves confirmation in a prospective trial. The evaluation of concentration-response relationships in our 29 cases was statistically powered to find only strong associations. In addition, our estimation of LEV exposure derived from Bayesian fitting of a population pharmacokinetic model is probably less accurate than would have been direct peak and trough measurements. Conclusions regarding less prevalent outcomes (e.g. mortality) or more complex analyses (e.g. multivariate logistic regression) are limited by the number of cases. Adverse events ascertainment suffers from the retrospective assessment. Thirdly, the loading doses oriented around our local guidelines recommending 30 mg/kg prevented tests with as much as 60 mg/kg recommended by some newer guidelines (Glauser et al., 2016). Further studies might clarify whether a dose-dependency of LEV efficacy would be revealed at those higher levels. The strength of the study is the prospective collection of clinical data in a registry having a robust internal validity (being run by the same investigators since several years), the detailed information regarding LEV doses, and the integration of LEV plasma concentrations in a validated pharmacokinetic model to overcome the bias resulting from variability in plasma sampling.

In conclusion, we identified no clear association between LEV exposure and therapeutic response of SE patients after LEV loading doses, even using a population pharmacokinetic approach to compensate the variability in LEV dosing and plasma sampling. These findings leave open the question of the usefulness of therapeutic plasma concentration monitoring of LEV in SE, in analogy with LCM. For further studies and general clinical practice, a standardised protocol for plasma level sampling applying consistent timing from last dosing, e.g. peak levels, might be of importance.

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Figures and tables

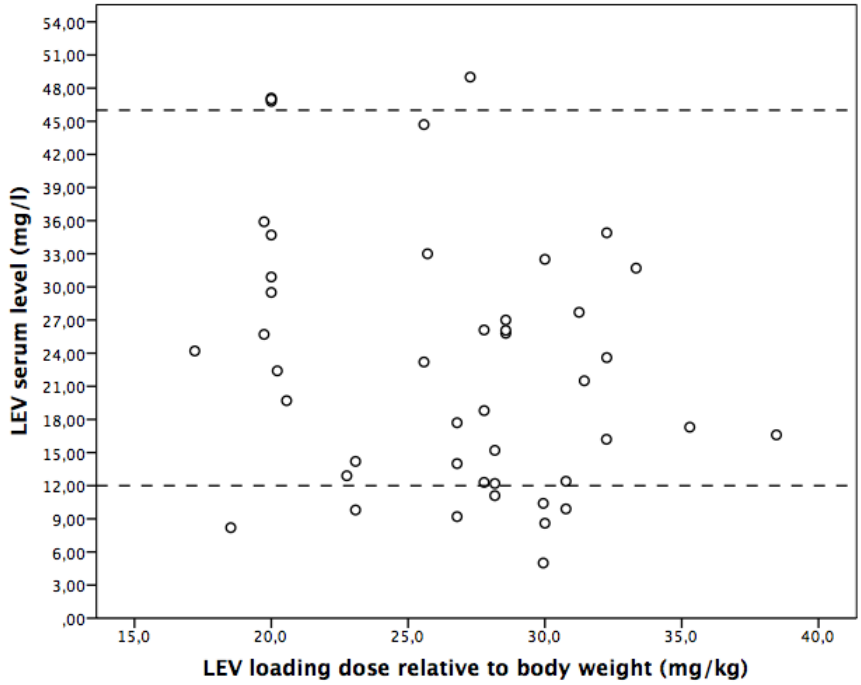

Figure 1: Measured plasma levels and loading dose related to body weight. Dotted lines represent the reference range of 12-46-mg/l containing 37 (82%) of measured plasma levels, with 4 (9%) below and 1 (3%) above it. No correlation between plasma levels and loading dose is found (p=0.84).

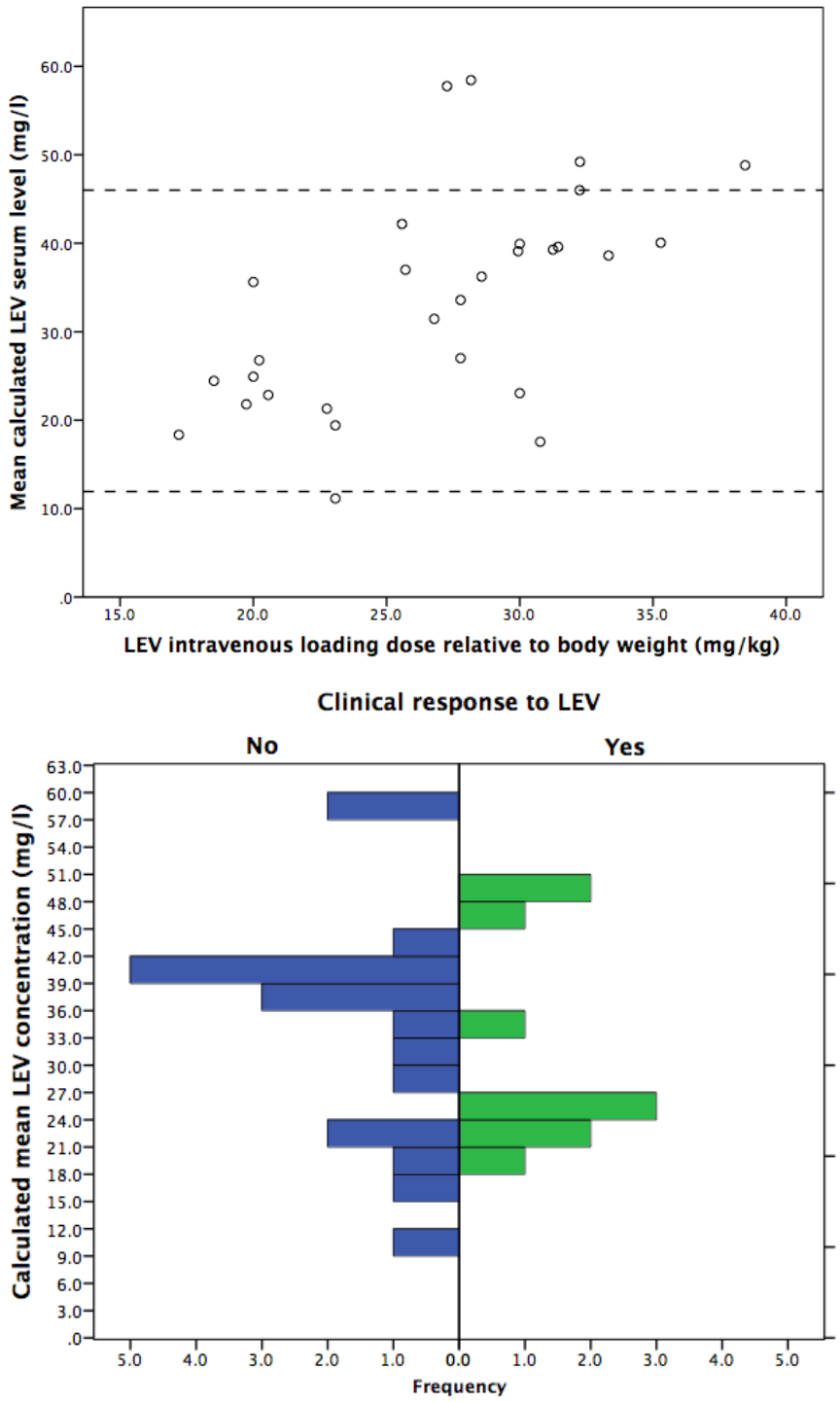

Figure 2a and 2b: Correlation between calculated mean LEV concentration and loading dose per mg/kg (2a; $p<0.001$, Spearmann) and according to clinical response (2b; $p=0.58$, U-test).

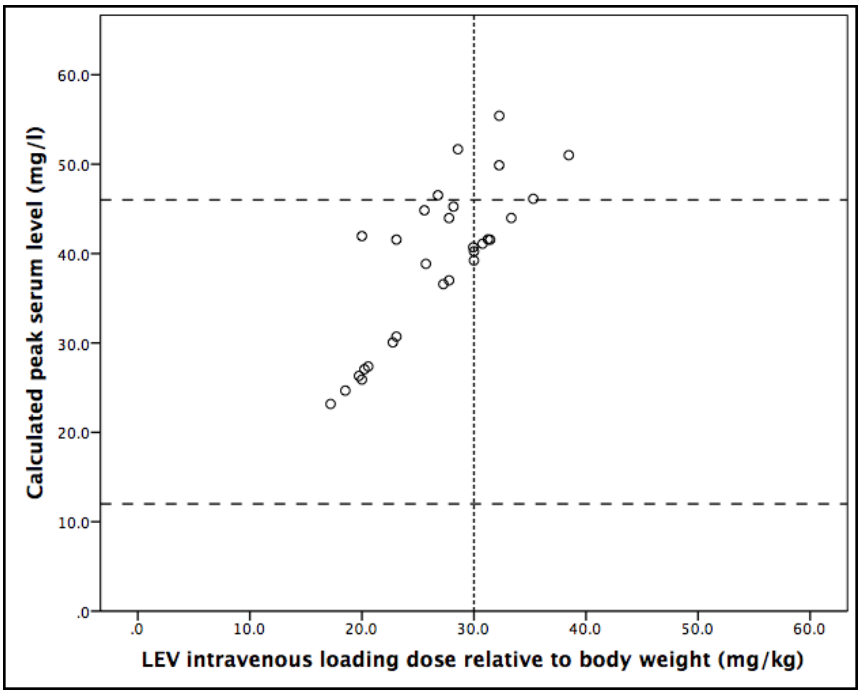

Figure 3: Distribution of the 29 peak plasma levels estimated by Bayesian maximum likelihood approach according to the loading dose (mg/kg).

Guidelines and reference	Year	Recommended doses	Equivalent relative to body weight (70kg)
European Federation of Neurological Society (EFNS) (Meierkord et al., 2010)	2010	**1000-3000mg**	14-42 mg/kg
Neurocritical Care Society (NCS) (Brophy et al., 2012)	2010	**1000-3000mg**	14-42 mg/kg
American Epilepsy Society (AES) (Glauser et al., 2016)	2016	-	**60mg/kg**

Table 1: Comparison of the recommended LEV loading dose from 3 SE guidelines according to the year of publication.

Clinical Characteristics	**All (n=29)**	**Responders (n=10)**	**Non-responders (n=19)**	**p-value**	**Test used**
Age - years Median (range)	73 (47-89)	75 (47-89)	73 (59-78)	0.43	U
Gender - males n (%)	13 (45%)	3 (30%)	10 (53%)	0.43	Fisher
Potentially fatal cause n (%)	16 (57%)	3 (30%)	13 (68%)	0.11	Fisher
Mortality at hospital discharge - N (%)	3 (10%)	2 (20%)	1 (5%)	0.27	Fisher
Favourable STESS of <3 – n (%)	7 (24%)	1 (10%)	6 (32%)	0.37	Fisher
SE duration before LEV - hours Median (range)	3.5 (0-1-99)	3.6 (0.1-42)	3.2 (0.5-99)	0.73	U
SE duration after LEV loading - hours Median (range)	12.0 (1.0-478.8)	6.8 (0.3-18.5)	29.3 (1.0-478.8)	**0.02**	U
Observation period-hours (range)	3 (0.3-50.8)	6.8 (0.3-18.5)	2.5 (0.3-50.8)	0.78	U
Total number of AEDs used Median (range)	3 (2-7)	2 (2-3)	4 (2-7)	**<0.001**	U
Previous LEV treatment	6 (21%)	2 (20%)	4 (13%)	**0.67**	Fisher
Position of LEV in the treatment sequence Median (range)	2 (1-3)	2 (2-3)	2(1-3)	0.12	U

LEV Loading dose - mg Median (range)	2000 (1000-3000)	1650 (1000-2500)	2000 (1500-3000)	0.08	U
Loading dose / body weight - mg/kg Median (range)	27.8 (17.2-38.5)	21.5 (18.5-38.5)	28.2 (17.2-35.3)	0.14	U
Cumulated LEV dose during SE (mg)	3000 (1000-10000)	2000 (1000-4500)	4400 (2200-10000)	**<0.001**	U

Table 2: Clinical characteristics of patients according to LEV response. Comparison between responders and non-responders is displayed to the right.

Calculated plasma level from the pharmacokinetic model	**All (n=29)**	**Responders (n=10)**	**Non-responders (n=19)**	p-value	Test used
Measured plasma level Median (range)	21.5 (8.2-49)	19.5 (8.2-46.8)	21.5 (8.6-49)	0.71	U
Mean calculated LEV plasma level during observation period (mg/l)	35.6 (11.2-58.4)	25.8 (19.4-49.2)	37.0 (11.2-58.4)	0.58	U
Maximum LEV plasma level after the loading dose (mg/l)	41.1 (23.5-55.4)	30.4 (24.7-55.4)	41.5 (23.2 -51.7)	0.36	U
Minimum LEV plasma level after the loading dose (mg/l)	19.6 (12.1-48.0)	14.6 (13.6-48.0)	20.5 (12.1-37.6)	0.37	U
Plasma level at the end of the observation period (mg/l)	33.7 (14.4-57.8)	25.4 (14.4-46.6)	36.0 (15.4-57.8)	0.07	U

Table 3:
Characteristics regarding measured plasma levels and calculated LEV mean, peak and trough plasma level from the population pharmacokinetic model. Note that direct comparison of the 45 overall plasma levels between responders and non-responders is not applicable because the number of patients (n) is lower than the number of plasma levels.