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Levetiracetam circulating concentrations and response in status epilepticus

Matthieu Perrenoud [a], Pascal André [b], Thierry Buclin [b], Laurent A. Decosterd [c], Andrea O. Rossetti [a], Jan Novy [a,*]

[a] Neurology Service, Department of Clinical Neurosciences, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, Switzerland
[b] Division of Clinical Pharmacology, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, Switzerland
[c] Clinical Pharmacology Laboratory, Laboratory Department, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, Switzerland

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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). The aim of the study was to evaluate the response to LEV in SE, correlated exposure assessed by plasma concentration monitoring, as well as calculated exposure parameters.
Materials & methods: We retrospectively analyzed a SE registry, including patients since 2015 with at least one available LEV plasma level measured less than 36 h 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 nonresponders. Therapeutic response was defined as SE cessation within 24 h following LEV introduction without a need for additional antiepileptic drug (AED).
Results: We included 29 patients (45 plasma levels). Variability was salient in LEV loading doses (ranging between 17 and 38 mg/kg) and monitoring practice. There was 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; $p = 0.61$), 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 nonresponders.
Conclusions: Levetiracetam exposure does not seem to differ significantly between responders and nonresponders; greater exposure was not associated with better outcome. Loading doses of 30 mg/kg seem, however, appropriate to quickly reach the target exposure level. The short LEV half-life makes standardized sampling measurement necessary to obtain directly interpretable LEV levels.

1. Introduction

Status epilepticus (SE) is a neurologic emergency [1] that can lead to serious morbidity and mortality especially when prolonged [2,3]. Strong evidences support the use of benzodiazepines as first line treatment; the second line is based on weaker evidence and typically consists of nonsedative antiepileptic drugs (AEDs) given intravenously. The following three AEDs have been commonly prescribed for several years: phenytoin, valproate, and levetiracetam (LEV) [4–6], while lacosamide is also increasingly used [7].

Levetiracetam is a broad-spectrum intravenous AED available since 2007 in Switzerland, targeting the synaptic vesicle protein 2 (SV2a) [8]. It is eliminated mostly through the renal route, has a low potential for drug-to-drug interaction, and has mild induced sedation [9]; it is, therefore, one of the most widely prescribed AEDs in SE, and its use seems to be increasing [7,10].

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 patients with chronic epilepsy [11]. The ideal LEV loading dose is not established; there is a trend toward increasing doses in the guidelines shown in Table 1. Maintenance LEV dosage should then keep circulating concentrations between those boundaries. In our center, a loading dose of 30 mg/kg is recommended. Estimated drug exposure through LEV plasma concentrations may help to validate a rational loading dose capable of producing the desired exposure.

Our study aimed at evaluating the current use of LEV in SE and at clarifying the potential therapeutic interest of assessing LEV exposure in SE management. In particular, we looked for an association between LEV exposure (in term of plasma levels as well as calculated exposure parameters) and achievement of therapeutic response.

* Corresponding author at: Service de Neurologie BH07, CHUV, Rue du Bugnon 21, 1011 Lausanne, Switzerland.
E-mail address: jan.novy@chuv.ch (J. Novy).

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

Guidelines and reference	Year	Recommended doses	Equivalent relative to body weight (70 kg)
European Federation of Neurological Society (EFNS) [5]	2010	1000–3000 mg	14–42 mg/kg
Neurocritical Care Society (NCS) [4]	2010	1000–3000 mg	14–42 mg/kg
American Epilepsy Society (AES) [6]	2016	–	60 mg/kg

2. Materials and methods

2.1. Population

This is a retrospective analysis of our previously described prospective SE registry [12], 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 electroencephalography (EEG) (the latter being mandatory for nonconvulsive episodes). Status epilepticus is defined as a single seizure that lasts more than 5 min in the case of generalized tonic–clonic seizures, more than 10 min in the case of focal seizures, or shorter consecutive seizures without complete recovery between the episodes [1]. Episodes occurring in patients younger than 16 years old or postcardiac 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 h.

For every episode, detailed patients' demographics and body weight were prospectively collected, together with SE duration and clinical characteristics, including the presence of a potentially fatal etiology, as defined previously [13]. 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) [14], 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 h) 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 h before SE resolution. The interval between LEV loading and response (either end of SE for responders or introduction of another AED for nonresponders) was defined as the observation period.

2.2. Serum levels

We screened all patients who 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 h 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 and ammonium levels, and comedications were retrospectively collected. Levels were determined using ultra-performance liquid chromatography with tandem mass spectrometry [15]. 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 center (also prospectively included in the registry), in whom no LEV plasma levels were available.

2.3. Pharmacokinetic model

Levetiracetam plasma concentration values were interpreted based on a population pharmacokinetic model [16], 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 level, 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 Bayesian 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) [17].

Levetiracetam exposure was assessed with the following two parameters: plasma level measured within 36 h (obtained from the laboratory 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.

2.4. Statistics

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 with other available clinical characteristics using chi-square, Fisher, Mann–Whitney *U*, and Spearman tests, as required. Secondly, 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 etiology [13,18], in a binary logistic regression. Calculations were done with *SPSS version* 23.0 (IBM corp., Armonk, NY).

3. Results

3.1. Clinical characteristics and response to treatment

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

As an internal validity assessment, the 29 included patients were comparable with 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), favorable 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: 2nd versus 2nd; $p = 0.2$; *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 nonresponders are given in Table 2. There was no significant difference between both groups. Levetiracetam 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