

INTRAVENOUS LEVETIRACETAM AS SECOND LINE OPTION FOR STATUS EPILEPTICUS

AURELIAN UNGUREANU¹, LUCA LIVIU RUS^{2*}, FELICIA GABRIELA GLIGOR², ANA LĂZĂROAE¹, LIANA PRODAN¹, CORINA ROMAN-FILIP^{1,3}

¹Department of Neurology, Academic Emergency Hospital Sibiu, 2-4 Pompeiu Onofreiu Street, 550166, Sibiu, Romania

²Preclinical Department, Faculty of Medicine, "Lucian Blaga" University, 2A Lucian Blaga Street, 550169, Sibiu, Romania

³Department of Neurology, Faculty of Medicine, "Lucian Blaga" University, 2A Lucian Blaga Street, 550169, Sibiu, Romania

*corresponding author: liviurus78@gmail.com

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Abstract

Status epilepticus (SE) and seizure clusters (SC) are life-threatening acute neurologic disorders and represent medical emergencies, requiring rapid and effective treatment. We studied retrospectively 67 patients admitted in our Neurological Intensive Care Unit, with SE or SC between December 2011 and January 2016 and we analysed the efficacy and tolerability of intravenous (IV) administration of levetiracetam (LEV) for SE and SC. The indications for IV LEV as second line treatment were SE or SC unresponsive to IV diazepam and the presence of co-morbidities that made phenytoin administration unsafe. IV LEV was administered as second line therapy immediately after no response from 10 mg of IV diazepam, in a maximum dose of 3000 mg/day. Unresponsive patients or patients at risk required general anaesthesia. The cessation of seizures within 3 hours, relations between variables and adverse events were evaluated. In 86.9% of the cases (58 patients), SE stopped within 3 h. Our study showed that IV LEV is an effective treatment for refractory SE or SC of different etiology.

Rezumat

Statusul epileptic (SE) și crizele convulsive subintrante (SC) reprezintă urgențe neuro- logice majore care necesită tratament rapid și eficient. Studiul de față a evaluat eficiența și tolerabilitatea administrării intravenoase (IV) de levetiracetam (LEV) ca a doua opțiune de tratament în SE și SC refractare. Au fost analizați retrospectiv, 67 de pacienți tratați în Unitatea de Terapie Intensivă Neurologică a Spitalului Clinic Județean de Urgență Sibiu, România, în perioada decembrie 2011 – ianuarie 2016. Indicația de tratament cu LEV IV a fost reprezentată de SE și SC refractare la administrarea de diazepam IV la pacienții pentru care continuarea terapiei cu fenitoină ar fi fost nesigură din cauza comorbidităților. A fost analizată rata de oprire a crizelor după 3 ore, relațiile statistice dintre diferite variabile și prezența de reacții adverse. Pacienții neresponsivi la LEV IV sau cu risc ridicat de complicații au necesitat anestezie generală. În 86,9% din cazuri (58 de pacienți), SE și SC au încetat în decurs de 3 ore de la debut. Studiul de față dovedește că administrarea de LEV IV este eficientă și poate fi luată în considerare ca a doua linie de tratament în SE și SC.

Keywords: *status epilepticus*, seizure clusters, intravenous levetiracetam

Introduction

Status epilepticus (SE) is a serious, life-threatening pathology recognized as a neurological emergency with mortality up to 20% and, therefore, should benefit from prompt medical attitude and rapid resolution [8]. The treatment of SE and seizure clusters (SC) consists of a first line treatment represented by benzodiazepines, followed by phenytoin as a second-line treatment [4, 21]. Recent studies showed the efficacy of intravenous valproic acid (VPA) as a second-line option, stating that there are more opportunities of arresting the SE or SC, especially when administration is saddled by the side effects [15, 19]. Marketed under intravenous (IV) form from 2006, levetiracetam (LEV) has an unknown mechanism of action [24]. Pharmacological studies demonstrated that it modulates the synaptic vesicle exocytosis in the gamma-aminobutyric acid

receptors [5]. It has a relatively small volume of distribution (0.5 - 0.7 L/kg) with maximum concentration of 50.5 µg/mL [19, 24]. The rapid infusion was shown to develop a rapid increase to maximum concentration and with no supplementary side effects compared to the slow infusion or oral administration [7]. IV LEV has a good safety profile and a stable pharmacokinetic profile making it desirable for the treatment of SE as a second line option [18]. Until now, encouraging results have been so far supplemented by case reports and retrospective case series in adult and paediatric patients [1, 5, 11, 12, 17, 25].

The aim of the present study was to analyse the efficiency of IV LEV as a second line therapy in patients with SE or SC.

Materials and Methods

There were analysed, retrospectively, 67 patients admitted in the Neurological Intensive Care Unit diagnosed with SE or SC, between December 2012 and January 2016. The study was approved by the Local Ethical Committee and informed consents were obtained from the family members for all the patients. In order to analyse results, we used Graph Pad Prism version 6.0 (Graph Pad Software, Inc. California, USA). Random variables were described by their mean and standard deviation (SD). The normality of variables was tested with D'Agostino-Pearson test. Where the normality could not be demonstrated, the variables were tested with non-parametric tests. Ranked variables were correlated with Spearman rank bivariate correlation and group comparison was tested with Mann-Whitney U test. Statistical tests were significant if two-sided p - values was < 0.05. *Status epilepticus* was defined as prolonged seizure over 5 minutes and the refractory SE was considered if the second line of therapy failed. SC were defined as repeated generalized tonic-clonic seizures with or without regaining the state of conscience, with high risk for developing SE. Super-refractory SE was defined when the third-line therapy with one cycle of intravenous anaesthetics

proved ineffective [9, 21]. Types of SE were clinically classified as generalized (primary and secondary) and focal motor. We defined beneficial therapy if seizure free intervals were at least one hour long and the patient regained conscience.

Inclusion criteria and treatment protocol

We included patients with SE or SC unresponsive to the first line of therapy (IV diazepam 5 mg at a dose rate of 2 mg/min, repeated at 10 minutes). A load of IV LEV 500 or 1000 mg diluted in 100 mL 0.9% saline solution was first injected over 15 minutes or, respectively, 30 minutes. The maintenance dose of IV LEV was maximum 3000 mg/24 h. In case of refractory SE or SC, we administered thiopental 150 - 200 mg IV in *bolus*, followed by 5 mg/kg bw/h sustaining the dose for general anaesthesia up to maximum 72 hours. Where it was possible, we monitored the patients with long term electroencephalography to prevent non-convulsive SE. We analysed the evolution under treatment with interest in the SE or SC arrest within 3 hours, as well as general anaesthesia, adverse events and death.

Results and Discussion

Demographic and clinical data of the 67 patients included in the study are summarized in Table I.

Table I

Demographic and evolution variables in patients treated with IV LEV

	Total (67)	Total (%)
Gender		
Male	34	50.7
Female	33	49.3
Mean age (SD)	59 (19.7)	
Etiology		
Vascular	36	53.8
Encephalopathy (perinatal, CJD, hypoxic)	18	28.8
Tumour (primary and metastasis)	7	10.5
Other (SLE)	6	8.9
Type of seizure		
Primary or secondary	48	71.6
Generalized SE or SC		
Focal motor SE or SC	19	28.4
History of seizures		
Known epilepsy	22	32.9
<i>De novo</i> seizures	45	67.1
Evolution under treatment		
Seizures stopped within 3h	58	86.5
Mean hours to seizure stop (SD)	1.9 (1.53)	
Required anaesthesia	7	10.4
Adverse events		
Hepatic failure	1	1.5
Hepatic cytolysis	5	7.5
Respiratory distress	4	6.0
Aggravated respiratory insufficiency (COPD)	1	1.5

CJD = Creutzfeldt-Jacob disease; SLE = systemic lupus erythematosus; COPD = chronic obstructive pulmonary disease

The sex distribution in our cohort study was equal (49.3% women), with a group mean age of 59 years (SD $\pm$ 19.7). The predominant etiology of seizures was vascular (53.8%), followed by encephalopathy

(perinatal, hypoxic, Creutzfeldt-Jacob disease, toxic, 28.8%), tumoural (primary tumours or metastatic disease of central nervous system, 10.5%) and other (ex. systemic lupus with

neurologic manifestations, encephalitis, lymphoma). The majority (71.6%) seizure type was represented by primary or secondary generalized SE, followed by focal SE (28.4%). The main endpoint followed in the study was the SE arrest within 3 hours. The mean seizure duration on treatment with IV LEV until cessation was 1.9 h (SD $\pm$ 1.53) for the majority of patients (86.5%) seizure free within 3 hour from the onset.

Acute symptomatic seizures were present in 67.1% of the patients with a mean duration of seizures of 1.82 h (SD $\pm$ 1.56). Remote symptomatic seizures had a mean duration of 2.04 h (SD $\pm$ 1.51). There was no correlation between the two groups in the terms of SE duration ($p > 0.05$).

Age was associated with the etiology in our study group, as expected with the predominance of vascular etiology in older patients ($r = 0.31$, $p = 0.01$) (Figure 1).

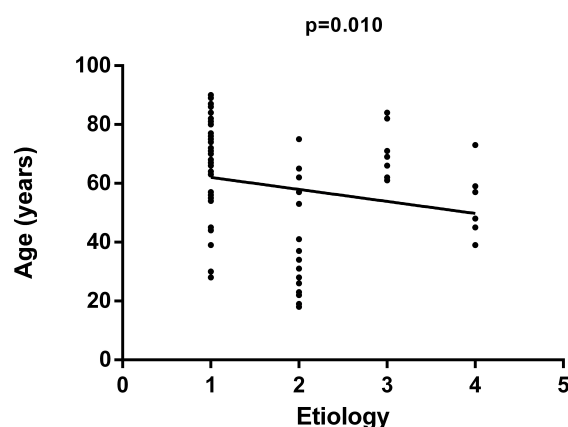


Figure 1.

The etiology was associated with age, in elderly patients predominating the vascular cause of SE; 1 - vascular; 2 - encephalopathy; 3 - tumour; 4 - others.

Age was associated with seizure type ($r = 0.28$, $p = 0.02$), older patients developing more often generalized SE, but, contrary to the expectations, necessitating less often general anaesthesia ($r = -0.25$, $p = 0.038$). No correlation was observed between seizure type and the duration of SE ($p = 0.058$), but a trend concerned the patients with focal SE who had longer mean duration. The group comparison for focal and generalized SE regarding the duration was not statistically significant ($p = 0.12$) (Figure 2). Seven patients (10.4%) required general anaesthesia because of the long duration of seizures, high frequency of SC or associated pathology in direct correlation with SE duration ($r = 0.3$, $p = 0.015$). No case of super-refractory SE was noted in our study group.

Adverse events were evaluated after initiation of IV LEV and only one (1.5%) patient developed hepatic failure, but it was attributed to underlying pathology.

In relation with LEV, transitory hepatic cytolysis was present in 7.5% of patients and respiratory distress after therapy was found in 4 patients (6%) and one aggravated chronic respiratory insufficiency (1.5%). We followed the patients after the cessation of SE and twenty three patients (34.3%) with a mean age of 62.5 years (SD $\pm$ 16.3) died from complications attributable to primary pathology (encephalitis, cerebral metastasis or primary tumour, lymphoma, infections).

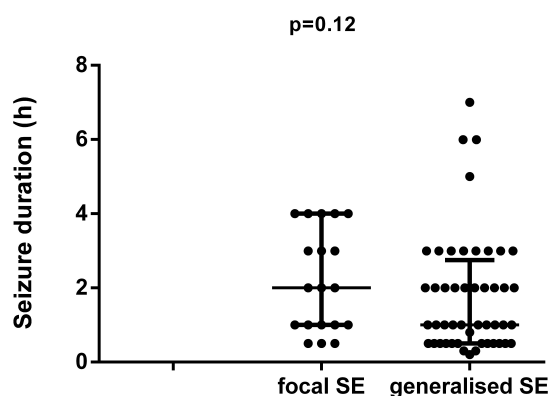


Figure 2.

Non-parametric group analyse of SE duration in patients with focal and generalized showing no significance between focal or generalised SE

The present results identify an efficient and rapid effect of IV LEV as second line therapy of severe SE, with a high rate of seizure freedom within 3 hours. Our mean duration until cessation of SE was 1.9 h (SD $\pm$ 1.53), indicating a very prompt response to IV LEV. It is known that acute symptomatic seizures followed by SE are more unfavourable in terms of outcome, especially associated with older age and metabolic or infectious complications [23]. In our group, there was no difference between the duration of SE in patients with *de novo* seizures and with known symptomatic epilepsy, translating that the response and outcome were similar in both groups.

The guidelines indicate benzodiazepines as drugs of choice in SE as first line and high doses of diazepam may cause GABA receptors to down regulate [3, 19, 21, 22]. This leads to accumulation and high serum levels and serious adverse events. The second line therapy is represented by phenytoin with very good results, although this efficacy is compromised by the adverse effects as it is proved that phenytoin can cause serious cardiorespiratory adverse events [21]. Our results are in accordance with previous studies, where IV LEV effect was similar or better than phenytoin. In a previous retrospective study we showed a positive effect of IV VPA as a second line treatment in SE or SC [16]. Several studies confirm the IV VPA efficacy

in SE, but these results are counterbalanced by the very strict titration rates and hepatic adverse effects. Both phenytoin and VPA are highly bound to proteins and along with hepatic metabolism they have implications in maintaining the therapeutic level constant and safe [14, 15, 21]. Another aspect is that both drugs may have serious interactions with other drugs administered in intensive care units [10, 20]. On the contrary, LEV is not metabolized in the liver and has no proven interactions with other medications and minimal cardiovascular and respiratory side effects or sedation [9, 13]. In what hepatic impairment is concerned, it is recommended to half the doses in patients with Child-Pugh C class cirrhosis [24]. Our rate of hepatic adverse events was small and no cardiorespiratory events were observed immediately or in the first 24 hours after the infusion.

Recently, a multicentre study found that IV LEV efficiency was present in 78.5% of patients, as a first line of treatment, when classical guideline drugs were contraindicated, but, on the contrary, were inferior in treating refractory status. As a second line of treatment, the results were consistent with previous researches [2].

Our study has limitations represented by the relatively small sample group and retrospective analyse, etiologic heterogeneity with substantial concomitant morbidities that could have biased the analysis. This warrants for further prospective and randomized trials.

Conclusions

In conclusion, our results showed the usefulness of IV LEV in SE with high rates of seizure freedom within three hours, with good tolerance and low rate of adverse events. The relative ease of administration, lack of serious side effects and the pharmacokinetic profile, make IV LEV an attractive alternative in the management of SE as second line therapy, especially in elderly patients with comorbidities and associated medication that may interact with classical drugs.

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Conflict of interest

No conflict of interest for any of the authors regarding this paper.

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