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Efficacy of intravenous levetiracetam as an add-on treatment in status epilepticus: A multicentric observational study☆

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ABSTRACT

Introduction: Treatment of status epilepticus (SE) has not changed in the last few decades, benzodiazepines plus phenytoin being the most common first line treatment. Intravenous levetiracetam (ivLEV) is a new antiepileptic drug with interesting properties for SE.
Material and methods: Efficacy and effectiveness of ivLEV in SE were assessed in an observational, multicentric and retrospective study. Efficacy was defined as cessation of seizures in the 24 h subsequent to starting ivLEV, with no need of any further antiepileptic drug. All patients were treated following the standard protocol (benzodiazepines plus phenytoin or valproate). ivLEV was used as add-on therapy, except in those cases with contraindication for the standard protocol, when it was administered earlier.
Results: 40 patients were included, 57% men, with a mean age of 63 years. The most common type of SE was partial convulsive (90%). ivLEV was effective in approximately half of the patients (57.5%), in a mean time of 14.4 h. ivLEV was used as add-on treatment in 26 patients (after benzodiazepines plus phenytoin, valproate or both) with an efficacy of 46.1%, and as early treatment (pretreatment with benzodiazepines or nothing) in 14 patients with an efficacy of 78.5% (p 0.048). Adverse events were observed in 15% of patients.
Conclusions: ivLEV was an effective antiepileptic drug for SE, but its efficacy depends on the timing of its administration, being more effective when used as early treatment, and less effective as add-on treatment.

1. Introduction

Status epilepticus (SE) is a medical emergency requiring intensive and prompt treatment in order to improve its outcome. SE affects 40 patients per 100,000 inhabitants each year,[1] with a mortality of around 20%.[1] The International Classification of Epileptic Seizures defines SE as "any seizure lasting for 30 min or longer or intermittent seizures lasting for more than 30 min from which the patient did not regain consciousness".[2] However, in clinical practice, the term "impending status epilepticus" is used. This term is defined as any seizure lasting 5 min or longer or intermittent seizures lasting more than 5 min, situation in which intensive treatment is mandatory in order to avoid a consolidated SE.

Etiology is the main factor determining the prognosis of SE,[3] although the moment in which treatment is started is also considered crucial. When an SE lasts more than 30 min, neuronal death can be produced due to the loss of several regulating mechanisms, and some previously helpful mechanisms may become harmful, impeding satisfactory resolution of the SE.[4]

Treatment of SE has not changed in the last few decades. Currently, benzodiazepines (BZD) (lorazepam or diazepam) followed by phenytoin (PHT) are still considered as first line

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treatment in the majority of the guidelines[3–7] with an efficacy of 70%.[8,9] All these guidelines follow the Treiman Veterans Study conducted in 1998 in which no differences were observed between treatment with lorazepam alone, diazepam plus PHT, or phenobarbital alone, whereas PHT alone was less effective.[10] Once first line treatment has failed SE is considered refractory. In refractory generalized tonic-clonic SE aggressive treatment is needed: coma with anesthetic drugs requiring orotracheal intubation and mechanical ventilation, usually in an intensive care unit.[3–7] The use of other antiepileptic drugs (AED) prior to the induction of pharmacological anesthesia should be considered in older patients, in patients with comorbidities and, specially, in other types of SE. In partial motor SE and in non convulsive SE previous treatment with other AED such as valproate (VPA) could be recommended. Recent studies, comparing the efficacy between VPA and PHT[11,12] have not found conclusive differences.

In recent years, some observational studies have shown the efficacy of levetiracetam (LEV) in treating SE. The first studies were done with oral presentation and including only a few patients,[13,14] while more recent series including a large number of patients, and using intravenous presentation (ivLEV), have also found it to be effective.[15–18] The results of these studies are promising with high responder rates. But, none of these studies classify patients according to etiology, SE type or other factors that can greatly affect the prognosis. To date no comparative study between ivLEV and VPA or PHT in patients with SE has been published.

In Spain the GELEVE group (Spanish Group for the study of ivLEV in SE) was set up with its main objective being to determine the efficacy and safety of ivLEV in patients with SE. A secondary objective of the group is to compare the efficacy of ivLEV administered as a first or second line treatment (after BZD) with ivLEV administered as third or fourth line treatment and to look for factors related to its efficacy such as etiology, loading dose, daily dose, etc. General accepted guidelines will be followed at all times and no changes in the usual clinical practice or in the protocols of each hospital will be accepted.

2. Material and methods

This is a multicentric observational study. We retrospectively reviewed the medical charts of consecutive patients diagnosed of SE and treated with ivLEV seen during the year 2008, in eight Spanish Hospitals: Hospital de Bellvitge, Hospital la Fe in Valencia, Hospital 12 de Octubre de Madrid, Hospital Josep Trueta in Girona, Hospital Clínico San Carlos de Madrid, Hospital Clínico Universitario in Santiago de Compostela, Hospital Universitario Virgen de la Arrixaca in Murcia and Hospital del Parc Taulí in Sabadell.

2.1. Definitions

SE was diagnosed according to the ILAE definition: (1) any seizure lasting for 30 min or longer or (2) intermittent seizures lasting for longer than 30 min from which the patient did not regain consciousness. When no motor signs were observed, for example in patients who suffered a seizure but did not regain consciousness afterwards, an EEG showing a diagnostic pattern of SE was needed to confirm the diagnosis.

An SE was classified according to its semiology into convulsive SE or non convulsive SE. Convulsive SE included not only generalized tonic-clonic status epilepticus but also partial complex or partial simple motor SE such as epilepsia partialis continua. We also classified SE according to the level of consciousness and the EEG into generalized SE, complex partial SE and simple partial SE.

ivLEV was administered in bolus twice a day. We considered that a loading dose was used if the first bolus was equal or superior to 1000 mg.

Efficacy was defined as cessation of seizures in the 24 h after starting ivLEV, with no need for any further AED. In patients with convulsive SE, cessation of seizures was considered to have occurred when the patient was conscious and free of convulsions. An EEG was performed to assess the end of SE in patients who did not regain consciousness.

2.2. Inclusion/exclusion criteria

All patients included were treated following a standard protocol (BZD plus PHT or VPA), so ivLEV was used as add-on therapy, except in those cases with contraindication for the standard protocol, when ivLEV could be used before. In the standard protocol the recommended loading doses of diacepam were 5–10 mg, of clonacepam were 1–2 mg, of PHT were 18–20 mg/kg and loading doses of VPA were 20–40 mg/kg. Patients who received smaller loading doses of PHT or VPA were retreated with an extra dose before entering in the study.

No generalized tonic-clonic SE were included in our study, because ivLEV was administered only in stabilized patients with no respiratory or haemodynamic compromise due to the SE. In cases in whom anesthetic treatment was used prior to ivLEV, we considered that efficacy of anesthetic treatment would be confused with efficacy of ivLEV, so these patients were excluded.

We considered the following contraindications to this standard protocol: BZD were contraindicated in respiratory failure and Lennox–Gastaut syndrome. PHT was contraindicated in hepatic failure, disorders of heart rhythm and important unpredictable pharmacological interaction. VPA was contraindicated in hepatic failure and thrombocytopenia. In summary, ivLEV treatment was used as first, second, third or fourth line treatment.

We classified patients into two groups, depending on the treatment received: Early treatment, when ivLEV was administered after BZD (or before in case of severe contraindications to BZD) and Late treatment when ivLEV was administered after BZD plus PHT or VPA or both.

Anoxic myoclonic SE (because of the implicit poor prognostic) and patients treated with LEV at home, except if the loading dose was higher than the daily dose used at home, were excluded. We also excluded patients when the standard protocol was not followed for example those who received ivLEV after BZD without contraindications for PHT or VPA.

2.3. Variables

The following demographic variables were recorded: gender, age, concomitant illness, concomitant treatment and previous history of epilepsy. Other variables recorded were: semiology, etiology, previous AED used, ivLEV loading doses, daily LEV doses, efficacy of ivLEV, adverse events, SE resolution with other drugs and mortality.

We classified patients according to etiology into several groups. Acute symptomatic (which includes acute stroke, inflammatory diseases of the CNS, cranial trauma, and meningoencephalitis), remote symptomatic, tumoral, toxic-metabolic, due to changes/stop/noncompliance of antiepileptic treatment, genetic and indeterminate.

2.4. Statistics

Statistical analysis was performed using SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA). Univariate analysis was performed. In the univariate analysis categorical variables were analyzed using a one-tailed chi-square analysis (with Yates correction when warranted) and continuous data were analyzed using *t*-tests and ANOVA tests.