Simultaneous administration of lorazepam and levetiracetam in non-convulsive status epilepticus (SALLISE), followed by IV valproate: a prospective, randomized, placebo-controlled, double-blind pilot trial.

Introduction.

Lorazepam (LZP) is an established first-line anti-epileptic drug (AED) in the treatment of status epilepticus (SE). In the VA trial (1), LZP controlled almost 65% of generalized convulsive SE and 18% of subtle SE. Side effects of IV LZP include hypoventilation in around 10% and hypotension in around 25%. Following IV LZP, a second IV AED is administered to control SE, or to prevent recurrent SE. Phenytoin (PHT) is chosen as second-line therapy by a majority of neurologists (2). A disadvantage of IV PHT administration is the cardiovascular side effects, necessitating 1.) a slow administration over at least 30 minutes, and 2.) monitoring ECG and blood pressure during infusion (3). It is, therefore, recommended to transfer the patient to an emergency room or intensive care facility, further delaying adequate treatment of SE, which becomes more difficult to control as its duration increases. IV valproate (VPA) is an alternative as a second-line AED, which can be administered fast, without sedation, respiratory depression or hypotension, and has been reported to be effective in the treatment of SE (4-10). It has been reported that IV VPA can control up to 78% of status epilepticus, regardless of order of treatment. Levetiracetam (LEV) (Keppra®) is a new effective AED with few side effects, and an IV formulation is available. LEV was effective in an animal model of SE, and enhanced the anticonvulsant effect of diazepam (11). IV LEV was administered in a randomized, placebo-controlled safety and pharmacokinetic study. Single ascending doses of LEV administered by IV infusion (2000, 3000, 4000 mg over 15 min and 1500, 2000 and 2500 mg over 5 min) were evaluated in 48 healthy subjects in a randomized, single-blind, placebo-controlled study. Adverse events were primarily related to the central nervous system (dizziness (53%), somnolence (33%), fatigue (11%), headache (8%)). Safety profiles were similar for each dose level of LEV and for both IV infusion rates (12). Preliminary results of IV LEV in the treatment of SE in humans appear favourably (13-19).

The aim of our study was to assess the efficacy and side effects of IV LEV as first-line AED together with IV LZP.

Methods.

Inclusion criteria. We included adult male and female patients with non-convulsive SE (NCSE), and more particularly complex partial SE (CPSE) and SE in coma. NCSE was defined as a change in behaviour and/or mental status from baseline associated with EEG changes consistent with SE. We subdivided CPSE into CPSE in patients with epilepsy and CPSE de novo. We considered subtle SE as a subgroup of SE in coma. Subtle SE was defined as SE that evolved from convulsive seizures to seizures with minor motor manifestations, such as muscle twitches, tonic eye deviation and nystagmoid eye jerks, and ictal EEG changes.

Exclusion criteria. We excluded simple partial SE (SPS), absence SE and postanoxic myoclonus or myoclonic SE, organic or psychogenic pseudoseizures, and coma with the following EEG patterns: periodic lateralised epileptiform discharges (PLEDs), bilateral independent periodic lateralised epileptiform discharges (BiPLEDs), periodic
epileptiform discharges (PEDs), generalized periodic epileptiform discharges, stimulus-induced rhythmic periodic ictal-like discharges (SIRPIDs), and triphasic waves. Cases that were doubtful on electroclinical grounds, in whom a diagnosis of SE would only be made a posteriori after a therapeutic trial with anti-epileptic drugs, were also excluded. Prior treatment for seizures was not an exclusion criterion. Current treatment with levetiracetam was an exclusion criterion. Renal failure was not an exclusion criterion. Contraindications for administration of VPA, such as hepatitis, mitochondrial disease, pancreatitis, pregnancy and hepatic porphyria, were exclusion criteria.

Objectives. Our objectives were to assess whether IV LEV could be administered safely in the treatment of NCSE, whether it was efficacious in termination SE fast when administered together with IV LZP, and whether it was efficacious in preventing relapse within 12 hours after treatment.

Interventions.

We recorded demographic data (age, gender and body weight), history of epilepsy or SE, age of first seizure and features of the SE (duration, etiology and seizure type). We used the criterion of seven days to differentiate between acute and remote symptomatic causes. The acute physiology and chronic health evaluation on day 1 of the treatment of SE was recorded (APACHE II classification) (20, 21). Prior use of AEDs was recorded. We assessed outcome at day 30 using the Glasgow Outcome Scale (22): 1. no or minor disability, 2. moderate disability, 3. severe disability, 4. vegetative state, and 5. death.

After the diagnosis of SE, hypoglycaemia was excluded by fingerprick. An IV line was inserted in an arm vein, a blood sample was taken for haematology, biochemistry, toxicology and arterial blood gases. Respiration was assessed and oxygen 10 L/min was administered if required. Vital sign, including temperature, pulse, blood pressure and respiration were assessed every 5 minutes. An oxymeter was applied and cardiac monitoring was performed. The Glasgow coma scale was assessed. Thiamine was administered in case of alcohol withdrawal. Continuous videoEEG monitoring was recorded, and recurrent seizures were assessed within 12 hours after treatment. The APACHE score was determined on the day of SE. EEG technicians and neurology residents received training session to recognise the different SE types, and an EEG course in the recognition of EEG patterns.

All patients received standard first-line treatment for SE during EEG recording. In our protocol, we gave IV LZP 0.05 mg/kg over 5 minutes followed by VPA 30 mg/kg IV over 5 minutes. Patients were randomly assigned to treatment with IV LEV 2500 mg (100 mg/ml in 5 mL ampoules) diluted in 100 ml 0.9% NaCl over 5 minutes or IV placebo (100 ml 0.9% NaCl without LEV) over 5 minutes given together with IV LZP. Vital signs, including blood pressure, pulse and respiratory rate were assessed before treatment, after administration of IV LZP plus IV placebo/LEV, and after administration of IV VPA. In this protocol, we have reduced the dose of LZP from the standard 0.1 mg/kg in view of side effects, including hypotension and hypoventilation in around 20% of cases. If SE was not controlled, other AEDs were given at the discretion of the treating neurologist. There was no repeated administration of Keppra IV after 12 hours.

Outcomes.
During the study, there were three evaluations of seizure activity: 1.) immediately after IV administration of LZP and placebo/LEV, 2.) immediately after IV administration of VPA, and 3.) 12 hours after treatment.

**Primary outcome.** The primary outcome was responder rate immediately after IV administration of LZP and before administration of VPA comparing the group that received placebo versus the group that received LEV.

**Secondary outcomes.** Secondary outcomes were responder rate 1.) immediately after IV administration of VPA and 2.) 12 hours after IV administration of LZP and VPA comparing the group that received placebo versus the group that received LEV. Further secondary outcomes were side effects and Glasgow Outcome Scale 30 days after treatment comparing the group that received IV placebo versus the group that received IV LEV.

**Sample size.**

This trial was conceived as a pilot-study, for which 80 patients were available. Based on this sample size, using a one-sided Fisher exact test with alpha=5%, the study had 80% power to detect a difference between 15% (placebo group) and 42% responder rate at the first evaluation. To detect a difference between 15% and 25%, 430 patients would be needed. In these power analyses, the stratified character of the study was not taken into account, due to lack of information on the prevalence of SE type and on homogeneity of the effect over the strata.

**Randomization.** The clinician first stratified the patients according to SE type into CPSE or SE in coma. The patients were then randomized to receive IV LEV or IV placebo to achieve equal numbers of patients receiving LEV and placebo in each SE group. An independent pharmacist numbered placebo and LEV vials from 1 to 80 according to a computer generated randomization list with 4 subject per block ([http://www.randomization.com/](http://www.randomization.com/)). The interventions were sealed in sequentially numbered identical containers according to the allocation sequence, and the lowest number available for the specified SE type was chosen to treat the patient.

**Blinding.** IV LEV 500 mg and placebo were kept in identical vials that were not distinguishable from each other. The administration of LEV versus placebo was blinded for the treating physicians and patients till the end of the study.

**Statistical analysis.**

For the primary outcome, the responder rate at the first evaluation, an exact p-value was calculated testing that the common odds ratio (common to the two strata) equals 1. The test was one-sided with alpha=5%. When the exact test for the homogeneity of this odds ratio was significant, strata-specific odds ratios were reported. Similar analyses were performed for each of the secondary outcomes, i.e. responder rate at the second evaluation and success rate at the third evaluation.

Ethical committee approval was obtained. Patients were informed that they had participated in a trial as soon as possible and were asked to sign an informed consent in which they consented that we could use the data for study purposes.

Reference List


