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Full Length Research Paper

Intravenous levetiracetam of hospitalized patients in Srinagarind Hospital

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Levetiracetam (LEV) is a fairly new antiepileptic drug with broad effectiveness in controlling seizures. Presently, there is limited clinical data worldwide. This study aims to add more clinical efficacy and safety data for intravenous LEV. Chart review was done in patients who received intravenous LEV at Srinagarind Hospital, Khon Kaen University, Thailand from August, 2010 to June, 2012. There were 48 prescriptions on 46 patients with a mean age of 56.75 years. The three most common causes of seizures were metabolic derangement, renal dysfunction, and hypoxic ischemic encephalopathy. Intravenous LEV was used for status epilepticus (SE) for 34 out of 48 prescriptions (70.8%) and non-SE 14 times (29.2%). The loading and maintenance doses of intravenous LEV were 1520.60 mg (range 1000 to 6500) and 1171.70 mg/day (500 to 3000). Seizure was controlled by intravenous LEV in 21 out of 34 prescriptions with SE (61.8%) and all patients with non-SE (100%). The overall mortality rate was 45.7% (21 out of 46 patients). The most common cause of death was sepsis with multiple organ failure (17 out of 21 patients or 81%). There was no obvious side effect of intravenous LEV in any patient. Intravenous LEV is effective and safe in seizure control particularly in patients with renal and liver dysfunction who had either SE or non-SE.

Key words: Levetiracetam, efficacy, safety, status epilepticus.

INTRODUCTION

Epilepsy is one of the most prevalent neurological diseases and a public health problem, because of its chronicity and necessity for continual treatment. The aim of the treatment is to prevent seizures and lessen unwanted side effects from antiepileptic drugs (AEDs). The decision on which AED is appropriate for each patient depends on other factors than just the epileptic type, such as pharmacokinetics, pharmacodynamics, comorbid diseases or concurrent drugs, factors related to each patient including sex, age, and liver and kidney function (Stein and Kanner, 2009).

Levetiracetam (LEV) is from a fairly new group of AEDs with a derivative structure of pyrrolidone and wide antagonizing mechanisms against seizures. LEV binds at a binding site at synaptic vesicle protein 2A (SV2A), and has a restraining effect on secretion of neurotransmitters in the presynaptic area (Lynch et al., 2004; Yang et al., 2007). It inhibits secretion of calcium from neuronal stores and activation of neurons without interfering with normal activation. Additionally, it has been shown that LEV does not involve inhibitory and excitatory neuro-transmission. Approved indications of LEV include:

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(1) use as a mono-therapy for partial onset seizure with or without secondarily generalization in patients of 16 years of age and over who are diagnosed as new epileptic patients, (2) use as an add-on therapy for partial onset seizures in adults and children of 4 years of age and over, (3) the use as an add-on therapy for myoclonic seizures in adults, in teenagers of age 12 and over having juvenile myoclonic seizures, and primary generalized tonic-clonic seizures in both adults and children from 4 years old (Lyseng-Williamson, 2011).

There are 2 types of available LEV forms at Srinagarind Hospital, namely, the 250 or 500 mg pills and the 100 mg/ml intravenous form. A loading dosage of intravenous LEV is 20 to 25 mg/kg and a maintenance dose is 20 to 25 mg/kg by continuous infusion over 24 h. Its properties are different from the conventional AEDs. Less than 10% of LEV binds to protein and does not use the cytochrome P450 or liver glucuronidation, resulting in fewer risks for interaction with other AEDs or other drugs. Prescriptions of LEV have increased, because of the potential use of both oral and intravenous drug administration together with patients' tolerance (Noachtar et al., 2008; Wu et al., 2009; Kwan et al., 2010). This study evaluated the efficacy of intravenous LEV in adult persons with epilepsy (PWE) at Srinagarind Hospital.

METHODOLOGY

The descriptive study is based on retrospective data from medical records of patients of 15 years of age and over who received intravenous LEV at Srinagarind Hospital, Khon Kaen University from August, 2010 to June, 2012. The data consisted of age, sex, seizures, comorbidities, indications, dosage, clinical outcome, and mortality.

Operation definition

Seizure control

Seizure control is defined clinically as no seizure occurrence after intravenous LEV treatment or without additional AED treatment or increasing the dose of LEV. "Uncontrolled" is defined by a seizure occurrence despite intravenous LEV treatment and additional AED intervention, relapse seizures, or requiring an increase of the dose of LEV.

Order of prescriptions of AED

The first line AED is the first drug a patient received to control seizures. If the seizure is uncontrolled, an additional AED is prescribed by attending physicians.

Causes of seizures

Renal dysfunction refers to the case where the patient has blood creatinine levels higher than 1.5 mg/dl. Hepatic dysfunction refers to the case where the patient has over 3 times of values of normal liver function or has evidence of cirrhosis. Metabolic disorder means an abnormality of blood components such as sodium, calcium, urea, or glucose, etc. Encephalopathy indicates post-cardiac arrest patients with hypoxic ischemic encephalopathy diagnosed by computed tomography of the brain (Legriel et al., 2008).

RESULTS

From August, 2010 to June, 2012, there were 48 prescriptions for 46 patients with a mean age of 56.75 years (range 15 to 91 years). Of these, 21 patients (45.7%) were male and 9 patients (19.6%) had a history of epilepsy (Table 1). Computed tomography of the brain was done on 36 patients (78.3%) with abnormal findings 28 times (77.8%). None of the patients had magnetic resonance imaging. Electroencephalograms were done 31 times and had epileptic discharge 20 times (64.5%). The three most common causes of seizures were metabolic derangement, renal dysfunction, and hypoxic ischemic encephalopathy (Table 2).

Intravenous LEV was used for status epilepticus (SE) for 34 out of 48 prescriptions (70.8%) and non-SE 14 times (29.2%). It was used as the first-and second-line AED in 9 (18.8%) and 23 times (47.9%); the other prescriptions were third- to eight-line treatment. The loading and maintenance doses of intravenous LEV were 1520.60 mg (range 1000 to 6500) and 1171.70 mg/day (500 to 3000). One patient who weighed 100 kg received the loading dose of 6500 mg (three times of the usual loading; 2500, 2000, 2000 mg). Seizure was controlled by intravenous LEV in 21 out of 34 prescriptions with SE (61.8%) and all patients with non-SE (100%). The overall mortality rate was 45.7% (21 out of 46 patients), 48.5% in SE group (16 out of 33 patients) and 38.5% in non-SE group (5 out of 13 patients) as shown in Table 3. The most common cause of death was sepsis with multiple organ failures (17 out of 21 patients or 81%). There were no obvious side effects of intravenous LEV in any patient.

DISCUSSION

Since August 2010, intravenous LEV has been used as an AED at Srinagarind Hospital. Presently, clinical data for LEV is limited. There are only 368 reported patients with intravenous LEV treatment, mostly from Europe. This study added to the efficacy and safety data of intravenous LEV on seizure control. Intravenous LEV was effective in non-SE compared to SE patients (100 versus 61.8%). Not surprisingly, seizure control was higher in non-SE patients. The mortality rates in both groups were still high (48.5% in SE group and 38.5% in non-SE group). The efficacy of intravenous LEV varied from 44 to 100% and 95% in seizure control of SE and non-SE patients (Table 4). Misra et al. (2012) reported that 10 out of 38 SE patients who received intravenous LEV died in hospital (26.3%) and 20 more patients were considered

Table 1. Demographic and clinical characteristics.

Characteristic	Number	Percentage
Number of patients	46	-
Men/Women	21/25	43.7/56.3
Number of prescription	48	-
Age (min.-max.) years	56.75 (15-91)	-
Previous history of epilepsy	9	19.6
Co-morbidity	51	-
Seizure type		
Non status epilepticus	14	29.2
Focal seizures	2	-
Complex partial seizures (CPS)	2	-
Generalized tonic-clonic seizures (GTC)	8	-
Myoclonic seizure	2	-
Status epilepticus (SE)	34	70.8
Convulsive SE (CSE)	15	-
Non-convulsive SE (NCSE)	19	-
CT brain	36	75
Abnormal	28	77.8
Normal	8	22.2
EEG		
No epileptic form discharge	6	19.4
Epileptic form discharge	20	64.5
Others	5	10.3

Table 2. Precipitating causes of seizures.

Cause	Number
Metabolic derangement	15
Renal dysfunction	14
Encephalopathy	14
Liver dysfunction	8
Acute ischemic stroke	6
Intracerebral hemorrhage	6
Post cardiac arrest	4
Drug induced seizure	4
Epilepsy	3
Old ischemic stroke	3
Autoimmune disease	3
Brain tumor	2
Thrombotic thrombocytopenia purpura	2
Unknown	2

Patients may have more than one precipitating causes.

possible deaths, because they left the hospital with deterioration. The mortality rate in SE in the Misra study was somewhat lower than in this study. For non-SE patients, the mortality rate in the study was still high. It was assumed that the high mortality rate in this study may be explained by high numbers of comorbidity conditions. All of the patients had at least one pre-existing condition. The overall numbers of comorbidities were 51 (Table 1). Even though the seizure control rate was quite high, the mortality rate was still high. The cause of death was not seizure related but mostly from septicemia and organ failure.

The clinical data on efficacy and order of intravenous LEV in SE are still controversial. Alvarez et al. (2011) reported that intravenous LEV was not as effective as sodium valproate for seizure control in SE after benzodiazepine treatment. In contrast, Gámez-Leyva et al. (2009) showed that intravenous LEV had potential effectiveness for SE treatment. The appropriate order of intravenous LEV in SE treatment is still obscure. In this study, intravenous LEV was used as the additional AED for SE. Almost half of SE patients received intravenous LEV as the third-line treatment.

Most patients (37 patients, 80.43%) had metabolic derangements, primarily renal or hepatic dysfunctions.

Table 3. Seizure stopping outcomes and mortality.

Characteristic	Times (no. of patients)	Outcome		Death (n)
		Seizure controlled, times	Uncontrolled seizures, times	
Status epilepticus	34 (33)	21	13	16
Non-status epilepticus	14 (13)	14	0	5
Total	48	35	13	21

Table 4. Previous reports of intravenous levetiracetam.

Study	Country	Population	Outcome (terminated seizure %)
Retrospective author			
Ruegg (2008)	Switzerland	50 (SE: 24, non SE: 19, Prophyl axis:7)	SE: 16/24 (67%), non SE: 18/19 (95)
Knake (2008)	Germany	18 SE	18/18 (100)
Moddel 2009	Germany	36 SE	25/36 (69)
Gamez-Leyva (2009)	Spain	34 SE	24/35 (71)
Berning (2009)	Germany	32 SE	30/32 (94)
Fattouch (2010)	Italy	9 SE	7/9 (78)
Aiguabella (2011)	Spain	40 SE	23/40 (58)
Alvarez 2011	Switzerland	58SE	30/58 (52)
Prospective author			
Misra (2011)	India	48 SE	36/48 (75)
Eue (2009)	Germany	43 SE	19/43 (44)

LEV is indicated and safer than other AEDs for these patients, because it does not have interaction with the cytochrome P450 isoenzyme (Lyseng-Williamson, 2011). There were four patients in the present series that were antibiotic associated seizures (3 patients received ceftazidime and 1 patient received cefazolin). All patients developed non-SE seizures, had renal dysfunction, and were controlled by intravenous LEV (Ozturk et al., 2009). Intravenous LEV may be an appropriate AED for this particular type of seizure.

The mechanism of action of LEV to control seizures is unknown. The possible mechanisms are the inhibition of voltage-dependent N-type calcium channels, facilitation of GABA-ergic inhibitory transmission through displacement of negative modulators, reduction of delayed rectifier potassium current, and/or binding to synaptic proteins which modulate neurotransmitter release. Intravenous LEV use may be increased in the future. There are some reported side effects including Steven Johnson syndrome, bullous pemphigoid, and aggravation of myoclonus and non-convulsive SE (Isoda et al., 2012; Karadag et al., 2012; Liu et al., 2012; Zou et al., 2012). Rare conditions such as hypersexuality are also reported after LEV use (Metin et al., 2012). Even though in this study, there were no serious complications of intravenous LEV. Side effects of LEV are still needed to be monitored.

Conclusion

Intravenous LEV is effective and safe in seizure control particularly in patients with renal and liver dysfunction who had either SE or non-SE seizures.

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