Original Article

Drug Use Review of Intravenous Levetiracetam in Patients with Epilepsy, Tertiary Care Hospital

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Background: Epilepsy is a current important health problem. Status epilepticus is a medical emergency condition which may be life-threatening, increased mortality rate and hospitalization. However, some patients with epilepsy could not control their symptoms and anticonvulsant medications have some adverse effects. Intravenous levetiracetam (ivLEV) is a new antiepileptic drug which its use tends to be increased.

Objective: To study the prescription pattern of ivLEV and its adverse drug reactions (ADRs) in hospitalized patients and to define the efficacy of iv LEV as first line treatment for status epilepticus.

Materials and Methods: This was a descriptive retrospective study to review medical records of all inpatients receiving ivLEV at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University during January 1st 2010 to December 31st 2014.

Results: During the study period, there were 406 hospital visits that met the study criteria. The average age of the patients was 54.32±20.36 years with nearly equal sex distribution. The indications of ivLEV were status epilepticus (22.4%), previous treatment with oral levetiracetam (9.6%), perioperative craniectomy/craniotomy (8.6%), and acute seizure with non-status epilepticus (59%). Most of the patients (63.3%) received ivLEV as first line treatment antiepileptic drug and the most loading dose range of ivLEV that the patients received was 500 to 1,000 mg/day (78.3%). All of the patients had been followed vital signs and plasma electrolytes. 98.5% and 45.8% of hospital visits had been monitored liver/kidney function and electroencephalogram (EEG), respectively. Adverse effects during the treatment of ivLEV occurred 0.98%, which were hypotension, drowsiness, and maculopapular rash. No major ADRs were detected in any patients after the ivLEV treatment. Regarding process indicators, overall seizure control rate was 76.4%, of which 35.2% and 85.9% were for the patients with status epilepticus and acute seizure with non-status epilepticus, respectively. ivLEV could be used as first line treatment effectively in patients with status epilepticus (80.2%). In the patients with renal impairment receiving adjusted dosage regimen ivLEV could be control seizure 73.1%.

Conclusion: The treatment of ivLEV was effective and safe for control seizure, including status epilepticus and acute seizure with non-status epilepticus. Thus, ivLEV could be the first line antiepileptic drug for the treatment of status epilepticus and brain surgery prevention. However, due to the high cost of the drug and the treatment course, there would be further study of cost-effectiveness.

Keywords: Levetiracetam, Epilepsy, Acute seizure, Status epilepticus, Drug use review, Inpatient

J Med Assoc Thai 2021;104(Suppl.1): S81-7
Website: http://www.jmatonline.com

Epilepsy is a current important health problem that can cause cerebral palsy, which is affect the patients and burden on the family and society. Most of the patients worldwide suffered from this common disease, including both human resources and economic aspects[1]. Seizure is a sudden, uncontrolled electrical disturbance in the brain. It can occur when one or more parts of brain has abnormal electrical signals or epileptiform activity that interrupt normal brain signals without a known or fixable cause[1].

Patients with epilepsy often have accidents, wounds and bruises on the body or head, broken skull or bone. They may also experience embarrassment, anxiety, low self-esteem, and suffered from depression. Some patients cannot study or work, make a burden to others, and costs a lot to maintain. Moreover, status epilepticus, a seizure that lasts for more than a brief period or any seizure lasting longer than 5 minutes, including continuous epileptiform discharges found on electroencephalogram (EEG), which is a medical emergency that life-threatening and significantly increase mortality rate and hospitalization[1,2].

From the data of Disbursement of hospitals in Thailand in fiscal year 2010, the patients over 18 years of age hospitalized with status epilepticus 2,190 hospital visits and 262 deaths (12%), which was the second highest cause of death among neurological diseases. In Srinagarind Hospital,

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How to cite this article:
Phenpinan S, Lertsinudom S, Tiamkao S. Drug Use Review of Intravenous Levetiracetam in Patients with Epilepsy, Tertiary Care Hospital. J Med Assoc Thai 2021;104 (Suppl.1): S81-7.
doi.org/10.35755/jmedassocthai.2021.S01.12281

Faculty of Medicine, Khon Kaen University, there were 35% of patient death from status epilepticus.

According to high mortality rate, uncontrolled seizures, and complication of treatment of status epilepticus, the new treatment and new antiepileptic drug would be studied[3]. Intravenous levetiracetam (ivLEV), a new antiepileptic drug, has been approved as adjunctive therapy for focal-onset seizure, myoclonic seizure, juvenile myoclonic epilepsy, and primary generalized tonic-clonic seizure in patients six years of age and older[4].

In cases of status epilepticus, ivLEV has not been approved. However, due to pharmacokinetics property that are low plasma albumin-binding, low liver metabolism, and low drug interaction, the patients can tolerate to the high dose and rapid intravenous administration (1,500 to 2,000 mg in 5 minutes) of the drug[4]. These making ivLEV attractive to be used for status epilepticus. The previous retrospective study showed that ivLEV was effective to control seizure in patients with status epilepticus (69%) and concluded that ivLEV was an antiepileptic drug for treatment status epilepticus effectively and safely[5].

Srinagarind Hospital, Faculty of Medicine, Khon Kaen University collected the data of ivLEV usage during 2005 to 2006, the results showed that there were 6-times increasing in drug use and tends to continue rising with the high expense of 9,583,680 Baht.

This study is conducted to review of ivLEV use for treatment in patients with seizures, in term of justification for use, process indicators, complications and their management, and outcome indicators. And use the obtained information as a basis for the development of drug use guideline appropriately. This will result in the most effective treatment and reduce the rate of adverse reactions from ivLEV. To review the usage and the prescription pattern of ivLEV in the justification of use, process indicators, complications and their management, and outcome indicators and to assess the efficacy of ivLEV as first line treatment of status epilepticus. The results of the study would be an important information to consider the usage of intravenous levetiracetam appropriately, which would result in the most effective treatment and reduced adverse drug reactions.

Materials and Methods

Study design

The descriptive retrospective study which describe the usage pattern of ivLEV, according to the justification of use, process indicators, complications and their management, and outcome indicators in the patients with epilepsy.

Scope of study

To review all inpatient medical records of the hospitalized patient who received ivLEV to control seizures at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University during January 1st 2010 to December 31st 2014.

Definitions

Seizure control indicated that seizures were under completely control and there were no recurrent seizures within 24 hours after treatment with ivLEV, without increasing the dose of ivLEV or adding other antiepileptic drugs.

First line treatment was determined the antiepileptic drug treatment order. The patients were administered ivLEV as the first drug treatment of seizure as soon as hospitalization. However, in the case of status epilepticus, ivLEV was administered after initial benzodiazepines treatment.

Renal function classified by creatinine clearance (CLcr) which is calculated by the formular below[6,7]:

$$\text{CLcr (ml/min)} = \frac{[140 - \text{Age (year)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine } \left(\frac{mg}{dl}\right)} \text{ (x0.85 for women)}$$

And adjust by body surface area (BSA) as:

$$\text{CLcr (ml/min/1.73 m}^2\text{)} = \frac{\text{CLcr (ml/min)}}{\text{BSA (m}^2\text{)}} \times (1.73)$$

Dosage adjustment in patients with renal impairment as shown in Table 1.

Study site

Srinagarind Hospital, Faculty of Medicine, Khon Kaen University.

Study population

All hospitalized patients who received ivLEV treatment.

Study sample

The hospitalized patients who received ivLEV treatment during January 1st 2010 to December 31st 2014.

Inclusion criteria

The inpatients ≥18 years' old who admitted at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University and received ivLEV treatment during January 1st 2010 to December 31st 2014.

Exclusion criteria

The patients who were not able to collect the information from medical records.

Research instruments

1) Medical records of the patients hospitalized

Table 1. Dosage adjustment of ivLEV according to renal function[7]

Estimated glomerular filtration rate (ml/min/1.73 m^2)	Dosage regimen	Total doses (mg/day)
50 to 80	500 to 1,000 mg q 12 h	1,000 to 2,000
30 to 50	250 to 750 mg q 12 h	500 to 1,500
<30	250 to 500 mg q 12 h	500 to 1,000

at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University.

2) Case report form.

3) Microsoft excel program.

Statistics and analysis

Statistical analysis, data of all eligible patients were analyzed using descriptive statistics. Baseline data and treatment of ivLEV are presented as mean (SD) or number (percentage). Process indicators and clinical outcome in those patients with and without status epilepticus are presented as mean (SD) or number (percentage).

Ethical approval

The study has ethical approval from the Khon Kaen University Ethics Committee for Human Research (HE591031) based on the Declaration of Helsinki and the ICH Good Clinical Practice Guideline.

Results

Medical records of all eligible patients were reviewed. During the study period, there were 432 hospital visits of all patients, however, 26 hospital visits could not be tracked the historical data. Thus, there were 406 hospital visits of 395 patients that met the study criteria.

Demographic data

From the data of 406 hospital visits, the average age of the patients was 54.32±20.36 years with nearly equal sex distribution. The Universal Coverage Scheme (UCS) was the main social health insurance program in most of patients (50%). The first three comorbidities were renal failure, cardiovascular disease and liver failure respectively. ivLEV was administered as the first line antiepileptic drug in 257 patients (63.3%) and was given at a dose between 250 to 3,000 mg/day, of those, most of the patient (78.3%) received loading dose ivLEV 500 to 1,000 mg/day (Table 2).

Justification for use

Indications of ivLEV were shown in Table 3. Which were status epilepticus 91 hospital visits (22.4%), previous treatment with oral levetiracetam 39 hospital visits (9.6%), perioperative craniectomy/craniotomy 35 hospital visits (8.6%), and acute seizure with non-status epilepticus 241 hospital visit (59.4%).

Process indicators

All of the patients had been followed vital signs and plasma electrolytes. The patients had been monitored liver/kidney function in 400 hospital visits (98.5%). The patients had been monitored EEG in 186 hospital visits (45.8%) which were positive for 26.4% and negative for 19.5% (Table 4).

In the patients who had been monitored the renal function, there were 338 hospital visits that eGFR <60 ml/min/1.73 m^2 (Table 2). However, only 62.3% of hospital visits that the patients had adjusted dosage regimen of ivLEV. Another 16% of hospital visits of the patients who were not received the proper regimen of ivLEV, the 64 hospital visits that the level of levetiracetam were remained on therapeutic range, as shown in Table 5.

Adverse effects during the treatment of ivLEV occurred 0.98%, of which there were cardiovascular adverse events which was hypotension 2 patients, neurological adverse event which was drowsiness 1 patient, and non-specific adverse effect such as maculopapular rash 1 patient.

Outcome indicators

The main clinical outcome was seizure control. In all of 406 hospital visits, the patients had seizure control in 310 hospital visits (76.4%). The seizure control rates in the status epilepticus and non-status epilepticus were 35.2% and 85.9%, respectively. ivLEV could control seizure as first line treatment 80.2% (Table 6). In 318 hospital visits of patients with renal impairment, there were 253 hospital visits that the patients received the adjusted dosage ivLEV and the seizure control rate was 73.1% (Table 7).

Discussion

Levetiracetam is a broad-spectrum antiepileptic drug and is approved as adjunctive therapy for several type of seizures in patients six years of age and older.

In the present study, the common indication for ivLEV treatment was acute seizure with non-status epilepticus (59.4%). The previous study[8] showed that ivLEV was used for status epilepticus 70.8% and non-status epilepticus 29.2%. This finding may be because of the greater number of patients in this study (406 vs. 48 hospital visits, respectively).

There were 35 patients (8.6%) who received ivLEV due to perioperative brain surgery prophylaxis. The authors found that ivLEV could be used to effectively prevent seizure in patients undergoing brain surgery (97.1%) correspond to Gokhale[9], which showed that ivLEV reduced the rate of postoperative seizure in brain surgery from 15 to 20% to 7.3%.

Most patients in the study received the appropriated dosage regimen of ivLEV with the average loading dose 971.3±438.2 mg/day (normally loading dose 1,000 to 2,000 mg/day) and the average maintenance dose 1,089.9±350.9 mg/day (normally maintenance dose 1,000 to 3,000 mg/day). However, Thongplew[10] showed that the average loading dose and maintenance dose were 1,520.60 mg/day and 1,171.10 mg/day, respectively. The dose of ivLEV used in the present study tend to less than the previous study, this finding may be due to the greater number of patients and the high ratio of patients with renal impairment (60.8% of hospital visits). Although 65 patients received an appropriated dose, the drug levels were within therapeutic range for 64 patients (98.5%), as shown in Table 5. These findings may imply that ivLEV may have a rather wide

Table 2. Baseline characteristics and treatments of patients who received intravenous levetiracetam

Patient characteristics	Number	Percentage
Number of patients/number of hospital visits	395/406	
Male	200	50.7
Female	206	49.3
Age; years (mean ± SD)	54.29±20.38	
Health benefit scheme		
Out-of-pocket (OOP)	18	4.4
Social security scheme (SSS)	3	0.7
Universal coverage scheme (UCS)	203	50
Civil servant medical benefit scheme (CSMBS)	157	38.7
Other scheme	25	6.2
Comorbidity		
None	8	2
Stroke	145	35.7
Hypertension	146	36
Diabetes	108	26.6
Hyperlipidemia	35	8.6
Cardiovascular disease	173	42.6
Brain tumor	70	17.2
Renal failure	247	60.8
Liver failure	157	38.7
Others	183	45.1
Renal function (eGFR: ml/min/1.73 m^2)		
>60	68	16.7
45 to 59	63	15.5
30 to 44	33	8.13
15 to 29	61	15.0
<15	90	22.2
Not available	91	22.4
Order of ivLEV administration		
First line	257	63.3
Second line	116	28.6
Third line	28	6.9
Fourth line	5	1.2
ivLEV loading dose (mg/day)		
500 to 1,000	318	78.3
1,001 to 1,500	74	18.2
1,501 to 2,000	8	2
>2,000	6	1.5

ivLEV = intravenous levetiracetam; eGFR = estimated glomerular filtration rate

therapeutic range, including the patients with renal impairment.

Intravenous levetiracetam could be used to control seizure of both status epilepticus and non-status epilepticus. However, ivLEV was more effective in seizure control in non-status epilepticus than status epilepticus (85.9% vs. 35.2%, respectively), which was similar to the studies of Thongplew[10] and Trinka[11].

Although the data of ivLEV as first line treatment is limited, however, the results in this study shown that

Table 3. Indication for intravenous levetiracetam treatment

Indication of ivLEV	Number of hospital visits (n = 406)	Percentage
Status epilepticus	91	22.4
Non-convulsive	29	7.1
Convulsive	62	15.3
Previous treatment with oral levetiracetam	39	9.6
Perioperative craniectomy/craniotomy	35	8.6
Acute seizure with non-status epilepticus	241	59.4

ivLEV = intravenous levetiracetam

Table 4. Process indicators

Monitoring parameters	Number of hospital visits (n = 406)	Percentage
Vital sign	406	100
Electrolytes	406	100
Serum creatinine/liver function test	400	98.5
Electroencephalography test	186	45.8
Positive	107	57.5
Negative	79	42.5

Table 5. Dosage adjustment of intravenous levetiracetam

Dosage adjustment (maintenance dose)	Number of hospital visits (n = 406)	Percentage
Dosage being adjusted appropriately	253	62.3
Dosage not being adjusted	65	16.0
Dosage being within therapeutic range	64	98.5
Dosage not being within therapeutic range	1	1.5
Not available	88	21.7

there were 63.3%of patients treated with ivLEV as first line treatment and 80.2% of those could control the seizure. Compare to other antiepileptic drugs in the previous studies, ivLEV is as effective as phenytoin and valproic acid for treatment status epilepticus after administered benzodiazepines[12,13]. Moreover, Misra[14] showed that ivLEV and lorazepam were not different in seizure control rate (76.3% and 75.6%, respectively). They concluded that ivLEV could be alternative to lorazepam for treatment status epilepticus in patients with respiratory failure and hypotension.

There were adverse events occurred in four patients, which might be the adverse drug reactions of ivLEV. Three patients who developed hypotension and maculopapular rash, were getting better after received 0.9% sodium chloride, antihistamine, and changed to another antiepileptic drug, respectively. One patient who developed drowsiness which was not a specific symptom and could not determine whether from seizure or adverse drug reaction. After added the other antiepileptic drug and closely monitored, the symptom of this patient was also improved. French[15] has studies the safety of ivLEV and found that the probable adverse drug reactions of ivLEV were drowsiness, fatigue, and dizziness which were occurred within the first month after start ivLEV treatment. The abnormal laboratory results of blood cells, hematocrit, hemoglobin, white blood cells, and neutrophils could be occurred. Moreover, emotional change and anxiety could be found especially in elderly or prior psychiatric symptom patients. In patients who developed side effects regarding to hypotension or rash, the previous study suggested that supplemental with intravenous fluid and antihistamine could improve the adverse events. However, in the present study, there were no major side effects were detected in any patients after the ivLEV treatment

Table 6. Clinical outcome of intravenous levetiracetam in all patients categorized by indication of use and order of administration (n = 406)

Indication of ivLEV	Seizure control (percentage)	Seizure uncontrol (percentage)
Status epilepticus (n = 91)	32 (35.2)	59 (64.8)
Non-convulsive status epilepticus	15	14
Convulsive status epilepticus	17	45
Previous treatment with oral levetiracetam (n = 39)	37 (94.8)	2 (5.2)
Perioperative craniectomy/craniotomy (n = 35)	34 (97.1)	1 (2.9)
Acute seizure with non-status epilepticus (n = 241)	207 (85.9)	34 (14.1)
Order of administration		
First line (n = 257)	206 (80.2)	51 (19.8)
Second line (n = 116)	89 (76.7)	27 (23.3)
Third line (n = 28)	14 (50)	14 (50)
Fourth line (n = 5)	1 (20)	4 (80)

ivLEV = intravenous levetiracetam

Table 7. Clinical outcome of intravenous levetiracetam in the patients with renal impairment categorized by dosage adjustment (n = 318)

Dosage adjustment (maintenance dose)	Seizure control (percentage)	Seizure uncontrol (percentage)
Dosage being adjusted appropriately (n = 253)	185 (73.1)	68 (26.9)
Dosage not being adjusted (n = 65)	54 (83.1)	11 (16.9)

which can cause life-threatening events.

There were some limited of this study. First, the definition of seizure control in the study implied only 24 hours after seizure cessation. Second, there was no correlation data with regard to disposing factors and treatment outcome. Third, some data were missing due to the retrospective nature of the medical record reviews. Finally, this study was not included the cost-effectiveness of ivLEV treatment.

Conclusion

The treatment of intravenous levetiracetam is effective and safe for control seizure, including status epilepticus and acute seizure with non-status epilepticus. This antiepileptic drug could also be used to prevent the seizure associated with brain surgery. Moreover, in patients who has comorbidities such as liver or renal impairment, it could be used as the first line antiepileptic drug to control their symptoms. However, due to the high cost of the drug and the treatment course, there would be further study of cost-effectiveness.

What is already known on this topic?

Intravenous Levetiracetam is effective and safe for control seizure, including status epilepticus and non-status epilepticus.

What this study adds?

Patients who has comorbidities such as liver or renal impairment could be used intravenous levetiracetam as the first line antiepileptic drug to control their symptoms because it effective and safety.

Acknowledgement

The researchers greatly appreciate and thank the Integrated Epilepsy Research Group for funding.

Conflicts of interest

The authors declare no conflict of interest.

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