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Intravenous levetiracetam treatment in Thai adults with status epilepticus

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Abstract

Background: The clinical data for intravenous levetiracetam in status epilepticus is limited particularly in the Asian populations. This study aimed to review the clinical use, efficacy, and outcomes of intravenous levetiracetam in Thai adults with status epilepticus. *Methods:* Clinical data of patients who were diagnosed as status epilepticus, aged over 15 years, and who received intravenous levetiracetam were retrospectively reviewed. The study was done at Srinagarind Hospital, Khon Kaen University, Thailand. The study period was between August 2010 and June 2012. Clinical data and outcomes were studied. Factors associated with a worse outcome of intravenous levetiracetam in status epilepticus were examined. *Results:* There were 34 prescriptions for intravenous levetiracetam in patients with status epilepticus. Approximately half of the patients were male (18 patients) and the mean age was 58.4 (range 15-91 years). All patients had at least one co-morbidity condition. The four most common causes of SE were electrolyte abnormalities or hypoglycemia with sepsis (14), renal dysfunction (12), hypoxic ischemic encephalopathy (11), and hepatic dysfunction (6). The seizure control rate was 61.8% (21 patients). There were 14 patients (41.2%) who were alive and had improvement at the time of discharge. Compared to those with worse outcome, there was no statistical difference in age, gender, type of status epilepticus, renal dysfunction, or second-line treatment except numbers of co-morbidity conditions. The worse outcome group had significantly higher numbers of co-morbidity conditions (p value 0.036).
Conclusion: Intravenous levetiracetam has good efficacy and may be a good option for status epilepticus.

INTRODUCTION

Status epilepticus (SE) is a condition with persistent seizure more than 5 minutes or the patient does not gain the consciousness during the interictal period. It is an emergency condition and requires prompt diagnosis and treatment for better outcomes.[1] The mortality rate of SE in Srinagarind hospital, Khon Kaen University was 35% compared to 20-25% in the US and 21.4% in France.[2,3] Clinical treatment guidelines and new drug development are needed to improve treatment outcomes of SE.[4,5]

Levetiracetam is a new antiepileptic drug (AED) in a group of pyrrolidones and has broad spectrum action for seizure control. Regarding pharmacokinetics, levetiracetam binds to serum proteins less than 10% and is not metabolized by the cytochrome P450 system or undergo glucuronidation in liver. It therefore has a low risk of drug interaction to other medications. Levetiracetam can also be given intravenously at a rapid rate. Presently, it has been used in SE, particularly in Europe. The seizure control efficacy was 44-100% for SE. Clinical efficacy and safety data, however, are limited in Asian populations. Due to the high cost of levetiracetam, it may have limited clinical applications in developing Asian countries. We report here the use of levetiracetam in a cohort of Thai SE patients.

METHODS

In this retrospective study, we reviewed medical charts of SE patients with an age of more than 15 years, who were treated with intravenous levetiracetam at Srinagarind hospital, Khon Kaen University, Thailand. The review consisted of patients treated between August 2010 and June 2012. The data abstracted included the baseline characteristics of patients, dose, seizure control, and outcome of the intravenous levetiracetam

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treatment. Data are presented by descriptive statistics and details for each patient. Clinical features of patients who had improvement at the time of discharge and those who died were compared. The Wilcoxon rank sum test was used to identify differences of continuous variables between those patients who were alive and had improvement with those who were not. Chi squared or Fisher Exact test was used to test differences of categorical variables between the two mentioned groups. The study protocol was approved by Khon Kaen University ethics committee for human research (HE551265).

Operational definitions of the study

Generalized convulsive SE was defined as recurrent convulsive seizures that may be overt or subtle, symmetric or asymmetric, and were associated with profound coma and bilateral, although often has asymmetric, ictal discharges on EEG.[6]

Non-convulsive SE was defined as status epilepticus with a change in behaviour and/or mental processes from baseline, associated or associated with continuous epileptiform discharges in the electroencephalogram, or in response to treatment.[7]

The primary goal for the outcome of the study was clinical seizure control. *Seizure control* was defined clinically as no seizure occurrence after intravenous levetiracetam treatment without additional AED treatment or increasing the dose of levetiracetam. *Uncontrolled* was defined by a seizure occurrence despite intravenous levetiracetam treatment and additional AED intervention, relapse seizures, or increasing the dose of levetiracetam. *Renal dysfunction* was indicated by serum creatinine levels more than 1.5 mg/dL, while *hepatic dysfunction* was defined as increased levels of serum transaminase by more than three folds or evidence of liver cirrhosis.

Co-morbidities were defined as pre-existing diseases, previous history and/or complication or adverse events developed before or following admission.

RESULTS

There were 55 prescriptions of intravenous levetiracetam during the study period. The medical record of 4 prescriptions could not be traced, and 34 prescriptions were used in SE treatment. Approximately half of patients were male (18 patients) and the mean age was 58.4 (range 15-91) years. Half of the patients (17 patients) had generalized convulsive SE (Table 1). All patients had CT brain scans; cerebral infarction and normal brain findings were the most two common findings in 18 and 10 patients. Electroencephalograms (EEGs) were done in 27 patients (79.4%). Epileptiform discharges were seen in 18 patients (66.7%) as shown in Table 2.

Five patients (14.7%) had a previous history of epilepsy. All patients had at least one co-morbidity (Table 1). The 4 most common causes of SE were electrolyte abnormalities or hypoglycemia with sepsis (14 patients), renal dysfunction (12 patients), hypoxic ischemic encephalopathy (11 patients), and hepatic dysfunction (6 patients).

The clinical features of the patients are summarized in Tables 1 and 3. The mean loading dose of intravenous levetiracetam was 1,545 mg (S.D.1,015) and the mean maintenance dose was 1,128 mg (S.D. 538.53). Intravenous levetiracetam was used as the first-, second-, third-line AED in 6, 11, and 9 patients.

The seizure control rate was 61.8% (21 patients). Two out of 6 patients who received levetiracetam treatment as the first-line AED were alive with good status at discharge (Table 3), while 12 out of 28 patients who received levetiracetam as other orders had good outcomes. There were 14 patients (41.2%) who were alive and had improvement at the time of discharge. Compared to those with worse outcome, there was no statistical difference in age, gender, type of SE, renal dysfunction, or second-line treatment except in numbers of co-morbidities. Co-morbidities were defined in the method section and are enumerated in Table 2. The worse outcome group had significantly higher numbers of co-morbidity conditions ($p = 0.036$) as shown on Table 4.

DISCUSSION

Intravenous levetiracetam was used in SE because it has less drug interaction, can be infused quickly and safely. Most SE patients in this study had co-morbidity of renal and hepatic dysfunction resulting in difficulty in using some AEDs.

The recommended dose of intravenous levetiracetam in SE in Thailand is 20-25 mg per kg as a loading dose over 30 minutes and 20-25 mg per kg for a maintenance dose with continuous infusion over 24 hours. One patient who weighed 100 kg (no. 16, Table 3), had a loading dose that fell outside the recommended dose.

Table 1: Baseline characteristics of the status epilepticus patients receiving intravenous levetiracetam.

No	Age	Sex	Previous epilepsy	Type of seizure	Diagnosis	Medication
1	85	F	yes	NCSE	ESRD, Vascular dementia	
2	82	M	no	NCSE	Recurrent embolic stroke, AF, AKI	Warfarin
3	69	F	no	CSE	Mitral valve stenosis, AF, Hypothyroidism	Warfarin, Levothyroxine
4	74	F	yes	NCSE	Infected CAPD,HAP,UGIB	Piperacillin/Tazobactam
5	69	F	no	NCSE	LN, septic shock, acute hepatitis	Meropenem, Vancomycin, Fluconazole
6	70	F	no	CSE	Liver abscess, Septic shock with multiorgan failure	Meropenem
7	49	M	no	CSE	Recurrent stroke, severe pneumonia, AKI on top CKD	Clopidrogrel, Dypiridamole
8	79	M	no	NCSE	TB meningitis, VAP, ESRD, ICM	IRZE, Meropenem, Amphotericin B
9	84	F	no	CSE	Melioidosis abscess, septic shock, ICH, UGIB	Piperacillin/Tazobactam,Meropenem, Ceftazidium,Co-trimoxazole, Fosfomycin
10	16	M	yes	NCSE	Epilepsy	
11	53	M	no	CSE	HBV cirrhosis, IgA nephropathy, AKI, post cardica arrest	Imipenam, colistin,colxacillin
12	20	F	no	CSE	SLE	Ceftazidium, Methylprednisolone
13	61	M	no	NCSE	ESRD, MCA infraction, Disseminated Tuberculosis ,septic shock	Ceftazidium, Meropenem, Levofloxacin,Amkacin
14	75	F	no	NCSE	HCV cirrhosis, Pleural effusion suspect hepatic hydrothorax, AKI	Ceftazidium , Meropenem, Piperacillin/Tazobactam
15	52	M	no	CSE	Knee arthritis, CKD, HCV cirrhosis	Cefazolin
16	52	M	yes	NCSE	CKD, HCV cirrhosis	
17	62	M	no	CSE	ESRD	Imipenem/Cilastatin
18	24	F	yes	CSE	Epilepsy	No
19	50	M	no	NCSE	ESRD, HCV cirrhosis , UGIB, septic shock	Vancomycin, Meropenem
20	60	F	no	NCSE	ESRD, Hypertensive urgency, infected CAPD	Ceftazidium, Piperacillin/Tazobactam, Meropenem

21	39	M	no	CSE	Aortic dissection, septic shock, AKI	Meropenem, Colistin, Vancomycin
22	65	M	no	CSE	Ruptured AAA, hemorrhagic and septic shock, cardiomyopathy, post cardiac arrest	Ceftazidium, Clindamycin
23	45	F	no	NCSE	SLE, pulmonary aspergillosis, hepatitis	Methylprednisolone, Meropenem, Anidulafungin, Voriconazole
24	83	F	no	NCSE	ESRD	Meropenem, Imipenem. Piperacillin/Tazobactam
25	58	F	no	NCSE	AIH, pancytopenia, AKI, UGIB, septic shock, AF	Cefoperazone/sulbactam, Piperacillin/Tazobactam, Amiodarone
26	50	M	no	CSE	TTP, alcoholic hepatitis	Vancomycin, Colistin
27	91	F	no	CSE	Septic shock	Gentamycin, Clindamycin, Ciprofloxacin, Fosfomycin, Cefoperazone/sulbactam
28	83	M	no	CSE	Acute on top chronic arterial occlusion, UGIB, AKI, hepatitis	Ceftriaxone, Meropenem
29	15	M	no	CSE	SLE with LN, pneumonia	Meropenem, Amphotericin B,Vancomycin
30	49	M	no	NCSE	Lung cancer, hepatitis, septic shock	Ceftazidium, Vancomycin, Cefoperazone/sulbactam, Colistin
31	50	M	no	CSE	Ischemic stroke, post traumatic brain injury, HAP	Levofloxacin, Cefoperazone/sulbactam, Colistin
32	29	F	no	NCSE	Splenic abscess, UGIB, rhabdomyolysis, septic shock	Meropenem, Ceftazidium,Levofloxacin, Amikacin, Co-trimoxazole, Fluconazole
33	73	F	no	CSE	Intertrochanteric fracture, CKD	Ceftriaxone, Ceftazidium
34	68	M	no	NCSE	TB peritonitis, HCV cirrhosis, septic shock	IRE, Piperacillin/Tazobactam, Metronidazole

AAA: Abdominal aortic aneurysm, AF: Atrial fibrillation, AIH: Autoimmune hepatitis, AKI: Acute kidney injury, CAPD: Continuous ambulatory peritoneal dialysis, CKD: Chronic kidney disease, E: Ethambutol, ESRD: End-stage renal disease, F: Female, HAP: Hospital-accquired pneumonia, HBV: Hepatitis B virus, HCV Hepatitis C virus, I: Isoniazid, ICH: Intracerebral hemorrhage, ICM: Ischemic cardiomyopathy, IgA: Immunoglobulin A, LN: Lupus nephritis, M: Male, MCA: Middle cerebral artery, R: Rifampicin, SLE: Systemic lupus erythematosus, TB: Tuberulosis, TTP: Thrombotic thrombocytopenic purpura, Z: Pyrazinamide)

Table 2: CT brain and EEG findings in patients who received intravenous levetiracetam for SE.

	No. of patients	%
CT brain	34	100
Cerebral infarction	18	52.9
Normal	10	29.4
Intracerebral hemorrhage	2	5.9
Brain atrophy	2	5.9
Diffuse brain swelling	1	2.9
Other: encephalomalacia	1	2.9
EEG	27	79.4
Epileptic discharge	18	66.7
No epileptic discharge	5	18.5
Encephalopathy	4	14.8

The efficacy or seizure control rate in SE by intravenous levetiracetam was 61.8%, while 14 patients (41.2%) survived and had an improved status at discharge. Even though there are several factors that may affect the seizure control and long-term outcome by intravenous levetiracetam in SE, this study shows that its use may be associated with good outcomes and high rate of seizure control. The seizure control rate in the same range as previous studies (Table 5).[8-19] The mortality rate of this study may be higher than most of the previous studies because our patients had high numbers of co-morbidities, and disease complications.

The number of co-morbidity conditions was the only significant factor between those patients with better and worse outcomes. Patients with a median of 3 co-morbidity conditions resulted in a worse outcome. Other factors were not different between better and worse outcome groups (Table 4). A previous study showed that epilepsy was the most common co-morbidity in 83 episodes of refractory SE (33/83 or 39.8%).[20] This suggests that known epilepsy may also be a risk factor for poor outcome. In the present series, only 5 patients had pre-existing epilepsy and 4 of them had good outcomes with intravenous levetiracetam (Table 3). It may indicate that intravenous levetiracetam may be appropriate for SE patients with epilepsy. Further prospective studies are needed to study the clinical predictors for better outcomes in SE treated by intravenous levetiracetam. The present study had a small sample size. In addition, data were not randomized and the retrospective collection resulted in missing data, no data on time to receive levetiracetam, and time to seizure control. EEGs were also not done in all patients.

Table 4: Comparison between patients who had improvement at the time of discharge and those who died

	Alive and improvement N = 14	Dead N = 20	p value
Median age (range), years	52 (15-85)	66.5 (20-91)	0.248
Male gender, N (%)	7 (50)	11 (55)	0.773
Convulsive status epilepticus, N (%)	9 (64.3)	8 (40)	0.296
Renal dysfunction, N (%)	7 (50)	12 (60)	0.820
Intravenous levetiracetam as a second-line antiepileptic drug after benzodiazepine treatment, N (%)	5 (35.7)	6 (30)	0.726
Median number of comorbidity conditions (range), numbers	2 (1-4)	3 (1-6)	0.024

Table 3: Details of the use of intravenous levetiracetam, laboratory results, and outcomes of the status epilepticus patients.

No	Line of medication treatment	Loading dose	Maintenance dose	CT	EEG	BUN	Cr	OC	Mortality
1	LEV	-	1000	CI	ND	59.8	7.2	SS	A/I
2	DZ P→LEV	1500	2000	CI	EP	54.4	6.8	SS	D
3	DZP→VPA→LEV	1000	1000	CI	ND	14.7	1.2	SS	A/I
4	LEV	1500	1000	CI	EP	81.6	4.8	SS	SM
5	DZP→VPA→TOP→Propofol→MDZ→LEV	-	500	N	CD	82.8	3.1	UC	SM
6	LEV	1000	2000	CI	ND	73.1	1.1	SS	SM
7	DZP→LEV→VPA→MDZ→Propofol	1500	1000	CI	NEP	78	3.9	UC	SM
8	LEV	1500	1000	CI	NEP	66.1	3.9	SS	SM
9	PHT→LEV	1200	1500	ICH	EP	51.9	1.9	SS	A/I
10	DZP→LEV	1500	3000	N	ND	11.3	0.8	SS	A/I
11	DZP→LEV→Propofol	1500	1000	BS	EP	32.5	3.2	UC	SM
12	DZP→PHT→VPA→TOP→PB→LEV→Propofol →DZP→atracurium	1500	2000	CI	EN	32.4	1.5	UC	S
13	PHT→LEV	-	1000	CI	ND	58.2	4	SS	S
14	DZP→TOP→VPA→LEV→PB→Propofol	1400	0	N	EP	21	2.9	UC	SM
15	DZP→LEV	1200	500	CI	EP	68.3	3.9	SS	A/I
16*	LEV	6500	2000	CI	EP	108.3	5.8	UC	A/I
17	DZP→VPA→LEV	1000	1000	N	EP	56.8	7.9	SS	A/I
18	DZP→TOP→LEV	1000	1000	E	EP	8.1	0.8	SS	A/I
19	LEV	1400	1000	ICH	EP	56.3	5.4	SS	SM
20	MDZ→PHT→VPA→DZP→LEV	1250	1000	N	EP	53.7	10.9	UC	A/I
21	DZP→PHT→MDZ→VPA→PB→TOP→Propofol→LEV	1500	1000	CI	EN	47.3	4.3	UC	SM

22	DZP→PHT→VPA→TOP→PB→LEV	1200	1000	CI	ND	83.3	9.9	UC	SM
23	DZP→LEV	-	1000	CI	NEP	52.7	3.1	SS	A/I
24	DZP→PHT→LEV	-	1000	CI	EP	68.5	2.6	UC	A/NI
25	DZP→PHT→LEV	-	1000	N	NEP	121.8	3.3	SS	A/NI/AA
26	DZP→PB→TOP→VPA→MDZ→LEV	2000	1000	CI	EP	21.5	0.7	UC	A/I
27	DZP→VPA→LEV	1000	1000	N	EP	37.8	3.8	SS	SM
28	DZP→PHT→LEV→TOP→MDZ	1500	1000	ICH	EP	86.2	4	UC	SM
29	DZP→PHT→PB→LEV	1900	1360	BA	ND	21.4	1.3	SS	A/I
30	DZP→LEV→MDZ	1000	1000	N	EP	172.8	8.4	UC	SM
31	DZP→PHT→LEV	2000	1000	N	EP	21.3	0.8	SS	A/I
32	DZP→LEV	1000	1000	CI	EP	42.4	1.3	SS	SM
33	VPA→LEV	1200	500	CI	EN	35.2	3.1	SS	A/I
34	DZP→TOP→LEV	1500	1000	BA	CD	17.7	0.8	SS	SM

Outcome (OC): SS-stop seizure, UC-uncontrolled seizure
Mortality: A-alive, SM-sepsis with multi-organ failure, S-stroke, I-improved, NI-not improve, AA- against advice
Computed tomography (CT): CI-Cerebral infarction, ICH-intra-cerebral hemorrhage, N-normal, BS-diffused brain swelling, E-encephalitis, BA-brain atrophy, Electroencephalogram(EEG):ND-no data, EP-epileptic discharge, CD- cortical dysfunction, NEP-no epileptic discharge, EN- encephalopathy BUN: Blood ureanitrogen, Cr: Creatinine
DZP: Diazepam, PHT: phenytoin, VPA: Sodium valproate, TOP: Topiramate, PB: Phenobarbital, LEV: Levetiratem, MDZ:Midazolam

*This patient weighed 100 kg and received 3 loading doses of 2500, 2000, and 2000 mg

Table 5. Summary of previous studies on intravenous levetiracetam treatment in status epilepticus. [7,9-13,16-21]

Study	Country	Population	Seizure control	Mortality No./percent
Retrospective				
Ruegg 2008	Switzerland	24 SE(50 Pt)	16/24(67%)	3/50(6%)
Knake 2008	Germany	18 SE	18/18(100%)	N/A
Beyenburg 2009	Luxembourg	8 SE	6/8(75%)	0
Moddel 2009	Germany	36 SE	25/36(69%)	6(16.7%)
Gamez-Leyva 2009	Spain	34 SE	24/34(70.5%)	3(8.8%)
Berning 2009	Germany	32 SE	30/32(94%)	2(6.3%)
Fattouch 2010	Italy	9 SE	7/9(78%)	0
Aiguabella 2011	Spain	40 SE	23/40(58%)	7(17.5%)
Alvarez 2011	Switzerland	58 SE	30/58(52%)	9/47(19.1%)
Prospective				
Misra 2011	India	48 SE	36/48(75%)	30(62.5%)
Tripathi 2010	India	41 SE	28/41(68.3%)	2(4.8%)
Eue 2009	Germany	43 SE	19/43(44.2%)	N/A

NA, not available

In conclusion, intravenous levetiracetam had good efficacy in this cohort of Thai patients and may be a good option for SE treatment particularly those with metabolic derangements.

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