

## Clinical outcomes of intravenous levetiracetam treatment in patients with renal impairment

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### Abstract

Intravenous levetiracetam has been approved for use as an antiepileptic drug, as well as in cases of status epilepticus. There are few reports that detail the clinical data and outcomes associated with this antiepileptic drug, particularly in patients with renal impairment. This was a retrospective analytical study conducted at Khon Kaen University's Srinagarind Hospital in Thailand. The study period was between January 1, 2010 and December 31, 2014. The inclusion criteria were that patients were over 15 years old, had renal impairment, and had received intravenous levetiracetam treatment. The main clinical outcomes were seizure control and mortality. Clinical outcomes were compared between those with and without status epilepticus. Mortality of patients with status epilepticus were compared in terms of seizure control and order of intravenous levetiracetam treatment. During the study period, there were 247 patients who met the study criteria. The average age of the patients was 58 years with nearly equal sex distribution. Of those, 90 patients (36.4%) had GRFs of less than 15 mL/min/1.73 m<sup>2</sup> and 60 patients (24.3%) received intravenous LEVE due to status epilepticus. The seizure control rates in the status epilepticus and non-status epilepticus groups were 36.7% and 88.7%, respectively (P<0.001). The mortality rate did not differ significantly between the two groups (33.3% vs 27.8%; P=0.418). There was no significant overall difference in mortality rate between

seizure-controlled and seizure-uncontrolled patients in the status epilepticus group. In the convulsive status epilepticus group, variations in terms of treatment order of intravenous levetiracetam and seizure control resulted in no significant difference in mortality rates (P=0.311). No major side effects were detected in any patients after the intravenous levetiracetam treatment. In conclusion, intravenous levetiracetam treatment was effective and safe in patients with renal impairment.

### Introduction

Epilepsy is a common disease in clinical practice. There were at least 70 million people worldwide suffered from epilepsy in 2010.<sup>1</sup> Untreated or uncontrolled epilepsy may lead to several serious conditions or complications including status epilepticus. The administration of antiepileptic drugs is the main method used in the treatment of epilepsy, and is aimed at to controlling seizures, avoiding side effects, and maintaining a good quality of life.<sup>2</sup> Currently, there are at least 155 antiepileptic products registered in Hong Kong, including new antiepileptic drugs such as levetiracetam and zonisamide.<sup>3</sup> The International League Against Epilepsy (ILAE) reported that further clinical studies are required to evaluate the relevant overall outcomes associated with antiepileptic drugs.<sup>4</sup>

Intravenous levetiracetam has been approved for use as an antiepileptic drug, as well as in cases of status epilepticus.<sup>5</sup> Although it is effective, the dosage for patients with renal impairment should be reduced.<sup>6</sup> Since levetiracetam clearance via kidney is 66% in patients with renal impairment, its half-life may last for 25 hours.<sup>7</sup> Additionally, body clearance decreases by 50% in patients with an estimated glomerular filtration rate of 30-50 mL/min.<sup>6</sup> Despite the widespread use of intravenous levetiracetam, there are few reports that detail the clinical data and outcomes associated with this antiepileptic drug, particularly in patients with renal impairment. This study aimed to evaluate the clinical use of intravenous levetiracetam in patients with renal impairment.

### Materials and Methods

This was a retrospective analytical study conducted at Khon Kaen University's Srinagarind Hospital in Thailand. The study period was between January 1, 2010 and December 31, 2014. The inclusion criteria

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were that patients were over 15 years old, had renal impairment, and had received intravenous levetiracetam treatment. The definition of renal impairment was based on creatinine clearance using the Cockcroft-Gault formula adjusted by skin surface area.<sup>8</sup> The study protocol was approved by the ethic committee in human research, Khon Kaen University (HE591031).

Medical records of all eligible patients were reviewed. Baseline characteristics, estimated glomerular filtration rate (GFR, mL/min), indications for intravenous levetiracetam treatment, details regarding intravenous levetiracetam treatment, and clinical outcomes were recorded. The main clinical outcomes were seizure control and mortality. The definitions for clinical terms were as follows: antiepileptic drug treatment order in cases of status epilepticus was determined after initial benzodiazepine treatment; seizure control indicated that seizures were under control and there were no recurrent seizures within 24 hours after treatment with intravenous levetiracetam; and death meant in-hospital mortality regardless of cause.

Statistical analysis. Data of all eligible patients were analyzed using descriptive statistics. Baseline clinical data and treatment with intravenous levetiracetam are presented as mean (SD) or number (percentage). Clinical outcomes were compared between those with and without status epilepticus using a Chi-square test, while mortality of patients with status epilepticus

were compared in terms of seizure control and order of intravenous levetiracetam treatment using a Fisher's Exact test. Statistical significance was defined as a P value less than 0.05. All statistical analysis was performed using STATA software version 10.1 (College Station, Texas, USA) and SPSS program version 16 (Chicago, Illinois, USA).

## Results

During the study period, there were 247 patients who met the study criteria. The average age of the patients was 58 years with nearly equal sex distribution. Of those, 90 patients (36.4%) had GRFs of less than 15 mL/min/1.73 m<sup>2</sup> and 60 patients (24.3%) received intravenous levetiracetam due to status epilepticus. Intravenous levetiracetam was administered as the first-line antiepileptic drug in 165 patients (66.8%) and was given at a dose between 1-2 gm/day in 226 patients (91.5%). There were 44 patients who received intravenous levetiracetam without dose adjustment for renal impairment, but 97.7% were given a dose that was within treatment dosage range (Table 1). The average expense per patient was 13,072 Baht (373.5 USD) which was due to the cost of intravenous levetiracetam, at 10,165 Baht (290.4 USD).

The seizure control rates in the status epilepticus and non-status epilepticus groups were 36.7% and 88.7%, respectively (P<0.001). The mortality rate did not differ significantly between the two groups (33.3% vs 27.8%; P value 0.418). The most common cause of death in both groups was sepsis (44 patients) as shown in Table 2. There was no significant overall difference in mortality rate between seizure-controlled and seizure-uncontrolled patients in the status epilepticus group (Table 3). In the status epilepticus group, variations in terms of treatment order of intravenous levetiracetam and seizure control resulted in no sig-

**Table 1. Baseline characteristics and treatment of patients with renal impairment who received intravenous levetiracetam (n=247).**

Factors	Values
Mean age (SD), years	58.0 (18.8)
Male sex	120 (48.6)
Glomerular filtration rate (GFR), mL/min/1.73 m <sup>2</sup>	
45-59	63 (25.5)
30-44	33 (13.4)
15-29	61 (24.7)
<15	90 (36.4)
Indications	
Status epilepticus	60 (24.3)
Non-status epilepticus	187 (75.7)
Naïve to levetiracetam	119 (48.2)
Currently on levetiracetam	19 (7.7)
Pre-operative prophylaxis	23 (9.3)
Others	26 (10.5)
Dose, mg/d	
500-999	17 (6.9)
1000-1999	226 (91.5)
2000-3000	4 (1.6)
Inappropriate dose by GFR	44 (17.8)
Dose within therapeutic range	43 (97.7)
Treatment order	
First-line	165 (66.8)
Second-line	64 (25.9)
Third-line	15 (6.1)
Fourth-line	3 (1.2)
Mean (SD) numbers of levetiracetam vials/patient	25.2 (24.6)
Mean (SD) of levetiracetam treatment, days	8.6 (11.3)

**Table 2. Clinical outcomes of patients with renal impairment who received intravenous levetiracetam (n=247) categorized by status epilepticus.**

Outcomes	Status epilepticus (n=60)	Non- status epilepticus (n=187)	P value
Seizure controlled	22 (36.7)	166 (88.7)	< 0.001
Death	20 (33.3)	52 (27.8)	0.418
Sepsis	14	30	
Gastric perforation/UGIB	2	1	
Severe metabolic disturbance	2	7	
Respiratory failure	1	4	
Sudden cardiac arrest/shock	1	8	
Hypovolemic shock	0	1	
Liver failure	0	1	

Data presented as number (percentage); UGIB: upper gastrointestinal bleeding.

**Table 3. Mortality of status epilepticus patients with renal impairment who received intravenous levetiracetam (n=60) categorized by treatment order of intravenous levetiracetam and seizure control (P=0.311).**

Order of intravenous levetiracetam	Seizures controlled (n=22)			Seizures uncontrolled (n=38)			Total
	Died	Survived	Total	Died	Survived	Total	
First line	4	9	13	8	10	18	31
Second line	4	1	5	3	10	13	18
Third line	0	4	4	0	4	4	8
Fourth line	0	0	0	1	2	3	3
Total	8	14	22	12	26	38	60

nificant difference in mortality rates, as shown in table 3 (P value 0.311). No major side effects were detected in any patients after the intravenous levetiracetam treatment.

## Discussion and Conclusions

Levetiracetam is a broad-spectrum antiepileptic drug and is approved as adjunctive therapy for focal-onset seizures, myoclonic seizure, juvenile myoclonic epilepsy, and primary generalized tonic-clonic seizures in patients six years of age and older.<sup>9,10</sup> The benefit of levetiracetam is its low drug interaction due to independent metabolism via the cytochrome P450 system.<sup>11</sup> However, in patients with renal impairment, dose adjustment is required.<sup>12</sup>

In this study, the most common indication for intravenous levetiracetam treatment was non-status epilepticus (119 patients or 48.2%), followed by status epilepticus (60 patients or 24.3%). There were 23 patients (9.3%) who received intravenous levetiracetam due to perioperative brain surgery prophylaxis. A previous study showed that intravenous levetiracetam reduced the rate of postoperative seizure in brain surgery from 15-20% to 7.3%.<sup>13</sup> Most patients received the appropriate dose for renal impairment (203 patients; 82.2%). Although 44 patients received an inappropriate dose, the drug levels were within therapeutic range for 43 patients (97.7%), as shown in Table 1. These findings may imply that intravenous levetiracetam may have a rather wide therapeutic range in renal impairment. Intravenous levetiracetam was prescribed as the first-line treatment at the highest ratio (66.8%) due to low drug interaction.<sup>11</sup>

Intravenous levetiracetam was more effective in terms of seizure control in the non-status epilepticus group than in the status epilepticus group (88.7% vs 36.7%). In this study, intravenous levetiracetam had a lower seizure-control rate than it did in a previous study.<sup>14</sup> A study conducted by Oman found that intravenous levetiracetam had a seizure-control rate of 82% in 22 status epilepticus patients. In our previous

study, the seizure-control rate of intravenous levetiracetam cases of status epilepticus was lower than that of sodium valproate (47.06%) but higher than phenytoin (21.62%).<sup>15</sup> These findings may be explained by differences in study population. Both previous studies were conducted in normal adults, but this study was performed in patients with renal impairment. This may indicate that intravenous levetiracetam may have lower efficacy in this setting. Note that mortality rates did not differ between status epilepticus and non-status epilepticus patients.

The overall mortality rate for the 60 patients with status epilepticus in the seizures-controlled group did not differ from that of the seizures-uncontrolled group (36.4% vs 31.6%), as shown in Table 3. Additionally, the order of intravenous levetiracetam did not affect the overall mortality rate (P value 0.311). As previously reported, factors associated with mortality in status epilepticus are varied, but the types of antiepileptic drugs administered is not among them.<sup>15-18</sup> The mortality rates in status epilepticus patients treated with phenytoin and sodium valproate were 29.73% and 11.76%, respectively (P value 0.189).<sup>15</sup> Older age or early treatment may be associated with status epilepticus mortality.<sup>16-18</sup> Further studies may be needed to confirm the results of this study in terms of order of intravenous levetiracetam treatment on mortality in status epilepticus patients.

There are some limitations to this study. First, mortality in this study was not specifically due to seizure and was recorded as in-hospital mortality. No long-term mortality rates were recorded. Additionally, definition of seizure control in this study implied only 24 hours after seizure cessation. Second, there was no correlation data with regard to the level of renal impairment and treatment outcomes. Third, some data were missing due to the retrospective nature of the medical record reviews. Most patients in this study (91.5%) received intravenous levetiracetam treatment between 1000-1999 mg/day despite almost equal of CKD level distribution (Table 1). These findings occurred because the recommended dose for those with GFR less than 50 is between

500-1500 mg/day (Table 4).<sup>19</sup> Finally, as mentioned earlier, predictors for mortality and seizure control were not studied.

In conclusion, intravenous levetiracetam treatment was effective in patients with renal impairment.

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**Table 4. Doses of intravenous levetiracetam renal impairment.**

Glomerular filtration rate (mL/min/1.73m <sup>2</sup> )	Doses (mg)	Total doses (mg)/day
50-80	500-1,000 q 12 h	1000-2000
30-50	250-750 mg q 12 h	500-1500
< 30	250-500 mg q 12 h	500-1000

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