

# Trends of Intravenous Antiepileptic Drugs Used in Patients at Srinagarind Hospital, Thailand

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**Objective:** Seizures are considered a major neurological emergency condition that requires appropriate treatment with an aim to enable the patient to control the seizures. Seizures are dangerous and may result in a high chance of death. Selection of antiepileptic drugs, especially the IV AEDs is very important in the course of treatment since this can partly contribute to the patient's ability to control seizures and the mortality rate from complications can be reduced. Thus, this study aimed at investigating the trend of usage of intravenous-administered antiepileptic drugs in the standard AEDs and new AEDs groups and finding the costs of drug use so as to obtain base data and methods for planning improvement of patient care system in the future.

**Materials and Methods:** This descriptive study was performed by retrospective data collection from the patients receiving IV antiepileptic drugs at Srinagarind Hospital from January 1, 2005 to December 31, 2016. The patients' drug use was collected from electronics database of Srinagarind Hospital's pharmacy section. The rates of IV AEDs use were studied and comparison was conducted to obtain the costs of the standard and new groups of IV AEDs used.

**Results:** The patients receiving IV AEDs totaled 9,021 cases, 4,777 being males (52.95%) and 1,734 cases were children younger than 15 years (19.22%). Most of these patients used their Universal Health The Coverage (5,347 cases, 59.27%). In 2016, the proportion of patients with epilepsy increased 2.2 times or 602 patients from 2005. When comparing the rate of standard AEDs use (Phenytoin, Phenobarbital, and Sodium valproate) with new AED (Levetiracetam), it was found that the use of standard AEDs decreased (100% in 2005 compared to 61.83% in 2016). The drug in the standard group with the highest decreasing prescription rate was Phenytoin (62.17% in 2005 compared to 45.38% in 2016, or a decrease of 16.79%). Nevertheless, when comparing the percentages of prescription, Phenytoin was still found to be the mostly chosen IV AED for the patients (45.38%), followed by Levetiracetam (38.17%) and Sodium valproate (10.38%). Comparison of the costs of IV AEDs prescribed shows yearly increase. The highest cost resulting from increase of prescription was found in Levetiracetam, at the cost of 154,455.50 USD or an increase of 52.45% followed by Phenytoin at the cost of 69,710.07 USD or an increase of 23.67%.

**Conclusion:** The research indicates that the trend of IV AEDs use was in new AEDs group, and their costs arising from increased prescription were also higher. This shows the changing trend in the selection of drugs by physicians. The result here can be used as the basic data for planning the service and care systems for the patients in the future.

**Keywords:** Trends, Intravenous antiepileptic drugs

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Seizure is an emergency condition of the neurological system that needs immediate attention since its correlation with mortality rate and brain disability is high resulting from shortage of oxygen during the seizure. If unattended and seizures are left to continue, brain cells will increasingly be damaged leading to detriment effect on brain and neurological system. Seizures may be caused by a number

of causes: seizures from brain injury, history of epilepsy, brain or neurological system infection, stroke, brain tumor, or metabolic disorders, etc<sup>(1)</sup>. Prescription of IV AEDs depends on indications from a patient's condition which include many factors, for example, patients unable to take oral medicine, patients receiving brain injury, patients using the antiepileptic drug before and after a neurological or brain operation, or patients having problems related to the gastrointestinal tract or neurological diseases where oral administration is not possible<sup>(2)</sup>. Another indication is the drug use in the case of status epilepticus (SE) and in patients whose seizures are unable to be controlled within 1 hour, which is called refractory status epilepticus (RSE)-the condition not responding to treatment and resulting in high

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chance of death<sup>(3,4)</sup>. Thus, SE is the condition requiring abrupt treatment because survival rate varies inversely with past time. AEDs used must be of the type with rapid action on seizures and hence IV AEDs are preferred. Therefore, the major principle for treatment of seizures is diagnosis followed by immediate treatment and patient care according to the standard guideline so that danger that could happen to the patient is reduced<sup>(5,6)</sup>.

In addition to quick diagnosis and practices according to the accurate seizure treatment guideline, selection of antiepileptic drug, especially the IV AEDs is very important in the treatment process. This may partially contribute to the patient's ability to control seizure and the mortality rate from complications will be decreased<sup>(7,8)</sup>. The intravenous-administered AEDs commonly used consist of Phenytoin, Phenobarbital, and Sodium valproate<sup>(3)</sup>, which are in the standard AEDs group. At present, however, development and studies have been conducted on the efficiency of the new AEDs group that can be used to treat SE, *i.e.*, Levetiracetam. The new AEDs have been increasingly introduced in many hospitals<sup>(9,10)</sup>. At Srinagarind Hospital, this drug group has been in use since 2010.

The present study thus aimed to investigate the trend of usage of intravenous-administered antiepileptic drugs in the standard AEDs and new AEDs groups and find the costs of drug use so as to obtain base data and methods for planning improvement of patient care system in the future.

## Materials and Methods

### Research design

This research was conducted based on the retrospective descriptive study method.

### Sample group

The patients who received an intravenous-administered antiepileptic drug at Srinagarind Hospital from January 1, 2005 to December 31, 2016.

### Methods

The data was collected of the drugs administered with the patients from the Pharmacy Section's electronics database, Srinagarind Hospital. The baseline data comprised sex, age, medical treatment rights, and treatment information such as types of drugs, quantities of drugs, drug costs, etc.

### Data analysis

The data was analyzed using descriptive statistics: frequency distribution, means, and percentages.

The research study was approved by Khon Kaen University's Human Research Ethics Committee and was granted an authorization number HE591050, dated February 9, 2016.

## Results

The obtained data indicated a total of 9,021 patients; 4,777 (52.95%) were males, 4,244 (47.05%) were females, and 1,734 (19.22%) were children younger than 15

years of age. Most of the patients (5,347, 59.27%) used their universal health security rights (the golden card), while many (2,130, 23.61%) used the official rights for medical care. When classifying the patients by the care units, most or 40.93% were found receiving medical treatment at the surgery unit, while 38.00% received the treatment at the medicine unit and 14.20% at the pediatric unit (Table 1).

The data from all of the patients from 2005 until 2016 reveal that patients prescribed IV AEDs could receive only one drug type or more. The mostly used drug was Phenytoin, which had been administered to 7,403 cases (69.59%), followed by Sodium valproate (1,276 cases, 11.99%) and Levetiracetam (1,212 cases, 11.39%) (Table 2). Comparison of patients classified by years from 2005 to 2016 depicts an increasing proportion every year. In 2005, orders were placed for all types of IV AEDs for 495 patients, whereas in 2016 orders were placed for 1,096 patients, or a 2.2-fold increase (Figure 1). The study of the numbers of inpatient receiving IV AEDs during the same period also indicates an increasing proportion every year, from 1.42% in 2005 to 2.43% in 2016 (Figure 2).

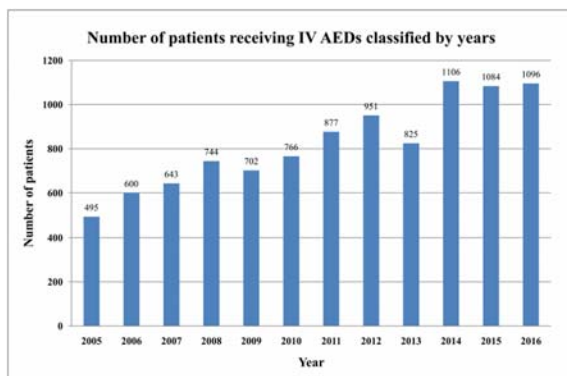
Comparison between the use of standard AEDs (Phenytoin, Phenobarbital, and Sodium valproate) and new AED (Levetiracetam) reveals that the number of patients using both AEDs groups increased every year, and Phenytoin

**Table 1.** The patients' baseline data

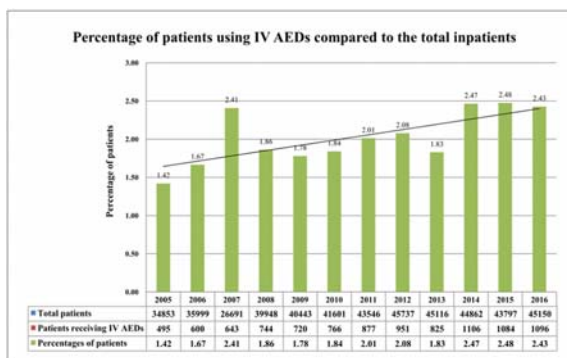
The patients' baseline data	Number of patients (Percentage)
Sex	
Male	4,777 (52.95)
Female	4,244 (47.05)
Age	
Lower than 15 years	1,734 (19.22)
15 years or higher	7,287 (80.78)
Right to medical treatment	
Universal Health The Coverage	5,347 (59.27)
Official right to medical care	2,130 (23.61)
Self-paying	1,068 (11.84)
Social security	476 (5.28)
Department	
Surgery	3,692 (40.93)
Medicine	3,428 (38.00)
Pediatrics	1,281 (14.20)
Others	620 (6.87)

**Table 2.** Data of intravenous drug use for patients classified by type of drug

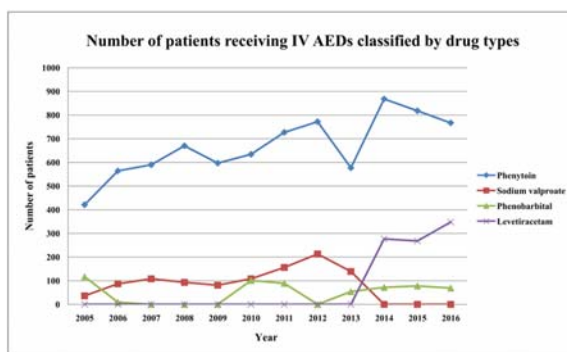
AEDs	n (%)
Phenytoin	7,403 (69.59)
Sodium valproate	1,276 (11.99)
Phenobarbital	747 (7.02)
Levetiracetam	1,212 (11.39)



**Figure 1.** Number of patients receiving IV AEDs (all 4 types) classified by years of hospital treatment



**Figure 2.** Percentage of patients using IV AEDs compared to the total inpatients.



**Figure 3.** Number of patients receiving IV AEDs classified by drug types.

was prescribed the most. In 2005, the number of patients receiving the drug was 421 cases, whereas in 2016, 767 cases were prescribed, showing a 346-case increase (41.89%). Similarly, Levetiracetam, a new AED group that was introduced in Srinagarind Hospital in 2010, was increasingly

being prescribed. In 2016, 348 patients were using this drug. Phenobarbital was the only drug for which prescription decreased (5.81%) (Figure 3). When the percentages of the patients receiving AEDs were taken into account, it was found that Phenytoin use reduced from 73.34% to 58.82% or a 14.52% decrease. Phenobarbital also had a decreasing trend (a 15.09% decrease), while the percentages of Levetiracetam prescription was increasing (to 26.69%) (Figure 4).

Comparison of the percentages of prescription of the 4 types of IV AEDs shows that in 2005, Phenytoin was prescribed mostly, i.e., 2,808 vials (62.17%), followed by Phenobarbital -999 vials (22.12%). Sodium valproate was the least used -710 vials (15.72%). (Note that before 2005, Levetiracetam had not been introduced in the hospital). In 2016, the highest prescription was still found for Phenytoin - 9,195 vials (45.38%). However, the percentage of Phenytoin decreased when compared to 2005, while Levetiracetam was the second type of drug with highest prescription, i.e., 7,734 vials (38.17%). The drug receiving the lowest prescription was Phenobarbital 1,231 vials (6.07%) (Table 3, Figure 5, 6).

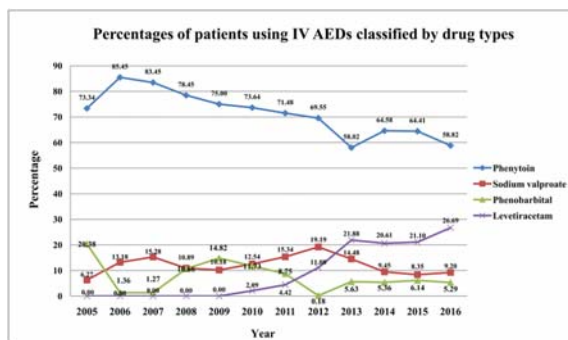
Investigation of the costs of IV AEDs prescribed reveals that the costs became higher every year, which corresponded to the increasing number of patients. When considering the costs of drugs in 2005, prescription amounted to the total cost of 45,856.60 USD whereas in 2016, it increased to 294,461.65 USD (an increase of 248,605.05 USD). Levetiracetam was the drug found with the highest orders (at the cost of 154,455.50 USD or an increase of 52.45%), followed by Phenytoin (at the cost of 69,710.07 USD or an increase of 23.67%) (Figure 7 and Table 3). However, when the data were taken to compare to compare of the costs of IV AEDs prescribed it was found that in 2005, Phenytoin received the highest cost, of 66.83%, which decreased to only 34.08% in 2016, while Levetiracetam was found to receive greater prescription (52.45%) (Figure 8 and Table 3).

## Discussion

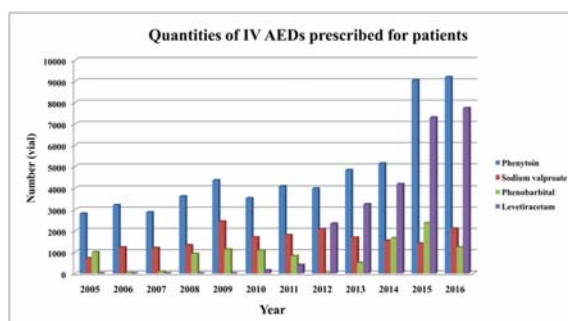
The survey conducted at northeastern hospitals on intravenous antiepileptic drugs including Diazepam, Phenobarbital, Phenytoin, and Sodium valproate shows that the community hospitals do not have all of these drugs, i.e., the availability of only 82.4, 7.8, 13.7, and 2.0%, respectively<sup>(11)</sup>, while Srinagarind Hospital has all of these drugs plus the new IV AED, i.e., Levetiracetam, which began to be available at the hospital in 2010. This study was conducted on the 4 types of IV AEDs: Phenobarbital, Phenytoin, Sodium valproate, and Levetiracetam. Since it was a retrospective study to collect the data from hospitals' electronics databases, there was a constraint related to indication of the patients' receiving Diazepam, of whether the drug was used to prevent seizures or for other conditions. Thus, Diazepam was excluded from the present study which means that one limitation of this study was the absence of indication of this IV AED use in patients resulting in inability to analyze what indications of any disease or condition there

**Table 3.** The rates of prescription of IV AEDs and the number of patients classified by drug types

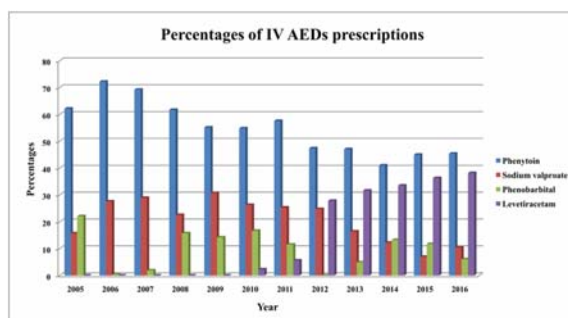
Drug types	Years											
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
<b>Phenytoin</b>												
Number of patients (case)	421	564	590	670	597	634	727	772	577	868	818	767
Quantities of drug (vial)	2,808	3,208	2,871	3,614	4,374	3,536	4,099	3,993	4,828	5,141	9,053	9,195
Drug cost (Baht)	1,055,808	1,206,208	1,079,496	1,358,864	1,644,624	1,329,536	1,541,224	1,501,368	1,815,328	1,933,016	3,403,928	3,457,320
<b>Sodium valproate</b>												
Number of patients (case)	36	87	108	93	81	108	156	213	139	127	106	120
Quantities of drug (vial)	710	1,225	1,198	1,321	2,434	1,694	1,802	2,084	1,684	1,534	1,403	2,104
Drug cost (Baht)	416,060	717,850	702,028	774,106	1,426,324	992,684	1,055,972	1,221,224	986,824	898,924	822,158	1,232,944
<b>Phenobarbital</b>												
Number of patients (case)	117	9	9	91	118	101	89	2	54	72	78	69
Quantities of drug (vial)	999	12	78	923	1,124	1,073	821	4	504	1,660	2,367	1,231
Drug cost (Baht)	107,892	1,296	8,424	99,684	121,392	115,884	88,668	432	54,432	179,280	255,636	132,948
<b>Levetiracetam</b>												
Number of patients (case)	0	0	0	0	0	18	45	123	210	277	268	348
Quantities of drug (vial)	0	0	0	0	0	146	398	2,343	3,247	4,202	7,300	7,734
Drug cost (Baht)	0	0	0	0	0	100,448	273,824	1,611,984	2,233,936	2,890,976	5,022,400	5,320,992
Total number of patients	495	600	643	744	702	766	877	951	825	1,106	1,084	1,096



**Figure 4.** Percentages of patients receiving IV AED classified by drug types.

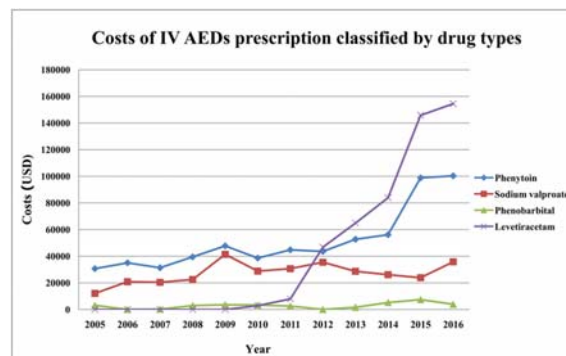


**Figure 5.** Quantities of IV AEDs prescribed from 2005 to 2016.

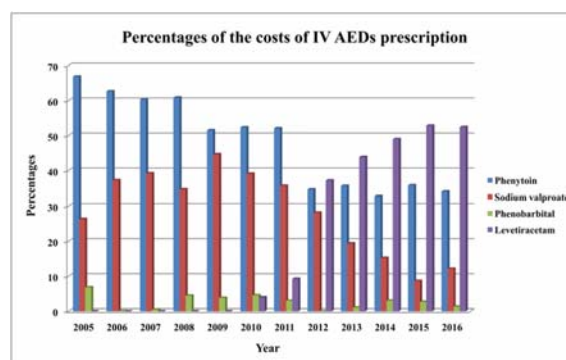


**Figure 6.** Percentages of IV AEDs prescription from 2005 to 2016.

might be. The data related to the period of drug use and treatment outcomes was also absent. The research findings could indicate that the number of patients receiving IV AEDs increased every year, which correlates to the data of Thailand<sup>(12-14)</sup>. There were more male patients than females, another indication which also corresponds to other studies<sup>(8,15,16)</sup>. In the present study, prescription of new IV AEDs had an increasing trend, at 38.17%, while the percentage of the standard IV AEDs decreased from 100% to 61.83%. This finding agrees with the study by Beuchat I et al<sup>(17)</sup>,



**Figure 7.** Costs of IV AEDs prescription classified by drug types (1 USD = 34.45 Baht to March 31, 2017 exchange rate).



**Figure 8.** Percentages of the costs of IV AEDs prescription classified by drug types.

which was conducted on the trend of prescription of IV AEDs by comparing between the new and standard IV AEDs groups from 2007 to 2016 and revealed that the percentage of prescription of the new group increased from 0.38 to 1.24% per seizure condition. The IV AEDs that were increasingly prescribed included Levetiracetam and Lacosamide, whereas Phenytoin was less prescribed, from 0.74 to 0.41% per seizure condition. The present study, however, found that the IV AED mostly chosen was still Phenytoin (45.38%), followed by Levetiracetam (38.17%). This finding differs from the study of Chiewthanakul in 2015, which indicated that Phenytoin was prescribed most by physicians, followed by Sodium valproate<sup>(16)</sup>. A study by Tiamkao in 2010 also indicated that the second selected type of drug after Phenytoin was Phenobarbital<sup>(8)</sup>, since Levetiracetam had not been available for use at that time in hospitals. When the costs of drugs were taken into consideration, even though Phenytoin was found in this study to be prescribed mostly, when compared to Levetiracetam, which was less prescribed, the costs emerged from prescribing Levetiracetam was much higher than Phenytoin at 84,745.53 USD. This is the issue to consider in the future in terms of



cost effectiveness of Levetiracetam in order to judge the worthiness of treatment, the management and control systems for drug use that corresponds to the treatment approach. In the present study, it was found that the trend of new IV AEDs use increased and the costs incurred were also high, denoting the changing trend in physicians' selection of drugs. Therefore, the results of this study can be used as the basic data for preparation and planning of patients' care and service systems in the future.

### What is already known on this topic?

Seizure is an emergency condition which requires appropriate treatment. IV AEDs are important way to stop the condition. Standard AEDs, such as Phenytoin, Phenobarbital, Sodium valproate are the first choice of treatment.

### What this study adds?

Rate of new AEDs (Levetiracetam) prescription is becoming higher which indicates the changing trend of treatment and also include the rising cost of therapy. This conclusion can be use as an guidance for planning and developing the treatment system in the future.

### Acknowledgements

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### Potential conflicts of interest

The authors declare on conflicts of interest.

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