A Retrospective Study on Clinical Outcomes and Safety of Letta (Generic Levetiracetam) in Patient with Epilepsy in Epilepsy Clinic

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Abstract

Background: Levetiracetam, a widely used broad-spectrum antiseizure medication, is available in both original and generic formulations. However, concerns persist regarding the efficacy and safety of switching between these formulations, particularly in patients with well-controlled epilepsy.

Objective: This study aimed to assess the treatment outcomes and safety of switching from the original levetiracetam (Keppra) to the generic formulation (Letta) in epilepsy patients at Srinagarind Hospital, Thailand.

Methods: A retrospective study was conducted from January 2021 to January 2024, analyzing the medical records of 191 epilepsy patients who transitioned from Keppra to Letta. Seizure frequency and adverse effects were compared before and after the switch.

Results: A significant increase in seizure frequency was observed in patients who had previously been well-controlled on Keppra ($p < 0.001$). While 69.63% of patients maintained seizure control on Letta, 30.37% experienced an increase in seizures. Three patients reverted to Keppra due to uncontrolled seizure and one due to aggressive behavior. Additionally, 16 patients required adjunct anticonvulsants. Adverse events occurred in 9.95% of patients, primarily somnolence and aggressive behavior.

Conclusion: The switch from Keppra to Letta resulted in decreased efficacy for some patients, especially those with previously stable seizure control. Clinicians should carefully consider potential risks and explore alternative therapies or revert

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to the original formulation for patients experiencing increased seizures.

Keywords: Levetiracetam, Letta, Keppra, Generic substitution, Epilepsy, Seizure frequency, Anticonvulsants.

Introduction

Levetiracetam is a second-generation broad-spectrum antiseizure medication known for its favorable pharmacological profile and low risk of drug interactions, making it suitable for patients with polypharmacy or multiple comorbidities.

For a generic anticonvulsant to be considered a substitute for the original, it must demonstrate bioequivalence within a range of 80% to 125%. Although studies have shown no significant difference in bioequivalence between original and generic levetiracetam[1,2], the transition from the original to the generic remains debated due to concerns about seizure control efficacy and potential side effects[3-5].

Antiepileptic drugs are classified by the MHRA into three categories based on therapeutic index, solubility, and absorption to guide decisions on whether continuity with a specific manufacturer's product is necessary. Levetiracetam, classified as category 3, generally does not require brand continuity unless specific concerns such as patient anxiety[6]. Studies from various countries have confirmed the safety and efficacy of switching from brand-name to generic levetiracetam[7,8].

According to Thailand's government policy on antiepileptic drug procurement, Srinagarind Hospital has adopted a policy to procure the generic form of levetiracetam, marketed under the name Letta, produced by MacroPhar in Suan Luang, Bangkok. This generic drug has been in use at Srinagarind Hospital since June 2021.

Currently in Thailand, there have been some studies investigating the efficacy and safety of generic levetiracetam.[9,10] However, the studied population is still limited, and conclusive results are yet to be determined. Additionally, the availability of generic drugs varies by hospital procurement, which underscores the purpose of this study is to investigate treatment outcomes and safety after switching from original levetiracetam to the generic brand Letta.

Patients and Methods

This retrospective study was conducted at Srinagarind Hospital, Khon Kaen University, Thailand, covering the period from January 1, 2021, to January 1, 2024. Medical records from the neurological outpatient department were analyzed, focusing on patients diagnosed with epilepsy. Participants included those initially treated with the original formulation of Keppra who were subsequently transitioned to the generic medication, Letta.

Inclusion criteria required participants to be at least 18 years old at the time of data collection. The exclusion criteria included individuals with chronic alcohol use disorder who continued consuming alcoholic beverages, patients with untreated brain tumors or tumors that had not been fully resected, individuals missing three or more follow-up appointments, and those unable to attend follow-up visits. A total of 344 data records of epilepsy patients treated with the generic formulation, Letta, were initially identified. However, 153 patients were excluded as they had not received the original formulation, Keppra, prior to this treatment. Ultimately, 191 cases met the study's inclusion criteria.

Data Collection

Data for this study were collected retrospectively from the medical records of patients initially receiving original levetiracetam and subsequently switched to generic levetiracetam treatment at Srinagarind Hospital. The following demographic and clinical information was extracted:

1. Demographic information:
   - Age
   - Gender
2. Medical history and pre-existing conditions:
   - Underlying disease
   - Other concurrent anticonvulsants
3. Seizure characteristics:
   - Type of seizures
   - Cause of seizures
4. Seizure frequency (the number of seizures per month):
   - Seizure frequency before switching to Letta: Seizure frequency was assessed during Keppra treatment for a minimum of 4 weeks prior to the switch.
   - Seizure frequency after switching to Letta: Seizure frequency was assessed 2-4 weeks post-switch.
5. Side Effects:
   - Adverse effects of Letta
6. Changes in anticonvulsant therapy:
   - Switch back to Keppra
   - Addition of other anticonvulsants
   - Switch to other anticonvulsant drugs
7. Dosage
   - Dosage of original levetiracetam (Keppra)
   - Dosage of generic levetiracetam (Letta)

Data Analysis

For categorical data, results will be presented as counts and percentages. For continuous data, descriptive statistics including the mean, standard deviation, median, minimum, and maximum values will be reported. The McNemar test will be used to compare seizure frequencies before and after the administration of Letta.

To simplify the statistical analysis, seizure frequency was categorized into two groups: no seizures per month and one or more seizures per month. Additionally, a separate analysis will be conducted for the subgroup of patients with high seizure frequency, focusing on those who experienced difficulty controlling seizures and were switched from original levetiracetam to the generic formulation.

Result

The study population consisted of 191 patients diagnosed with epilepsy, comprising 93 males and 98 females, with an age range of 18 to 97 years. The majority of patients experienced a generalized motor onset (40.84%), while unprovoked seizures were the most common etiology, representing 93.19% of cases. A detailed summary of the demographic and clinical characteristics is presented in Table 1.

Table 1: Demographic data of patients with epilepsy who receiving original levetiracetam and then switch to generic levetiracetam in the year 2021-2024 at Srinagarind hospital. (n=191)

Clinical characteristics	Number	%
Sex		
Male	93	48.69
Female	98	51.31
Age : Years		
Mean	51.88	
SD	21.43	
Range	18-97	
Comorbidity		
Total	111	100
Stroke	68	61.26
Hypertension	65	58.56
Diabetes mellitus	25	22.52
Chronic kidney disease	20	18.02
Traumatic brain injury	16	14.41
Psychiatric condition	10	9.01
Cirrhosis	2	1.80
Seizure onset		
Focal with awareness	35	18.32
Focal with impaired awareness	37	19.37
Generalized motor	78	40.84
Generalized nonmotor	7	3.66
Unknown	34	17.8
Etiology of seizure		
Acute symptomatic	13	6.81
Stroke	6	3.14
Central nervous system infection	3	1.57
Traumatic brain injury	2	1.05
Metabolic	2	1.05
Unprovoked	178	93.19
Remote or progressive symptomatic seizure	105	54.97
Unknown	73	38.22
Other antiseizure medication used during study.		
Levetiracetam monotherapy	93	48.69
More than one antiseizure medications	98	51.31

Clinical characteristics	Number	%
Type of other antiseizure medications		
Valproic acid	34	34.69
Phenytoin	14	14.29
Topiramate	27	27.55
Lamotrigine	31	31.63
Carbamazepine	14	14.29
Lacosamide	3	3.06
Perampanel	7	7.14
Phenobarbital	11	11.22
Clonazepam	19	19.39
Clobazam	14	14.29
Gabapentin	3	3.06

Among the 164 patients with well-controlled epilepsy initially treated with Keppra (85.86%), all remained seizure-free for at least one month. Following the switch to Letta, a generic formulation of levetiracetam, 133 patients (69.63%) continued to achieve effective seizure control. However, in a separate cohort of 27 patients (14.14%) who had experienced more than one seizure per month, the proportion of patients with multiple seizures per month increased to 58 (30.37%) after transitioning to Letta. This change represents a statistically significant difference in seizure control between the original and generic formulations of levetiracetam (p-value < 0.001), as summarized in Table 2.

Table 2: The comparison of seizure frequency before and after using Letta. (n=191)

	Before	After 2-4 weeks	p-value
Frequency of seizures per month			
0	164 (85.86%)	133 (69.63%)	<0.001
≥ 1	27 (14.14%)	58 (30.37%)	

In a subgroup analysis of the 27 patients with uncontrolled seizures (defined as more than one seizure per month), further classification revealed that 17 patients (62.96%) had 1-3 seizures per month, while 10 patients (37.04%) had 4 or more seizures per month. After switching from Keppra to Letta, the number of patients experiencing more than 4 seizures per month increased from 10 to 14 (51.85%). However, no statistically significant difference in seizure frequency was observed (p-value = 0.125), as shown in Table 3.

Table 3: A subgroup comparison of seizure frequency before and after using Letta in patients with more than one seizure per month. (n=27)

	Before	After 2-4 weeks	p-value
Frequency of seizures per month			
1-3	17 (62.96%)	13 (48.15%)	0.125
≥ 4	10 (37.04%)	14 (51.85%)	

Following the switch to Letta, four patients (2.09%) reverted to the original levetiracetam (Keppra) due to uncontrolled seizure and adverse effects. Three patients experienced an increase in seizure frequency that became difficult to manage, while one patient developed severe aggressive behavior. Upon switching back to Keppra, seizure control was restored to baseline levels, and the patient's mood returned to normal.

Among those who experienced an increase in seizure frequency after transitioning to Letta, 16 patients (8.38%) were prescribed an adjunct anticonvulsant instead of reverting to the original levetiracetam formulation. Most of these patients had one additional anticonvulsant added to their regimen to achieve effective seizure control. Another group of patients maintained seizure control but required an increase in the dosage of generic levetiracetam beyond the dose used with the original formulation. The average daily dose increased from 1,691.18 mg to 2,063.73 mg.

In the safety evaluation of generic levetiracetam, 19 patients (9.95%) reported adverse events following the transition to Letta. The majority of these patients experienced either somnolence or an exacerbation of aggressive behavior. Detailed data are presented in Table 4.

Table 4: Treatment outcomes after switching to Letta.

Clinical characteristics	Number	%
Seizure frequency before switching to Letta (per month)		
0	164	85.86
1	6	3.14
2	6	3.14
3	5	2.62
4	4	2.09
5	2	1.05
10	2	1.05
20	1	0.52
30	1	0.52
Seizure frequency after switching to Letta (per month)		
0	133	69.63
1	22	11.52
2	9	4.71
3	7	3.66
4	5	2.62
5	1	0.52
6	2	1.05
7	3	1.57
8	1	0.52
10	2	1.05
12	2	1.05
20	1	0.52
25	1	0.52
28	1	0.52
30	1	0.52

Clinical characteristics	Number	%
Switch back to Keppra		
Yes	4	2.09
No	187	97.91
Switch to other antiseizure medication		
Yes	5	2.62
No	186	97.38
The increasing number of antiseizure medications		
0	175	91.62
1	15	7.85
2	1	0.52
Adverse events after switch to Letta		
Total	16	8.38
Drowsiness	8	4.19
Aggression	7	3.66
Psychosis	1	0.52
Dosage of Keppra (original levetiracetam)	(mg/day)	
Average	1,691.81	
Median (Min:Max)	1000 (500:4,000)	
Dosage of Letta (generic levetiracetam)	(mg/day)	
Average	2,063.73	
Median (Min:Max)	1750 (500:4,000)	

Discussion

The efficacy and safety of generic levetiracetam were evaluated in outpatients at the Neurology Department of Srinagarind Hospital, Khon Kaen University, between 2021 and 2024. The study found that switching from the original levetiracetam (Keppra) to the generic formulation (Letta) resulted in a statistically significant increase in seizure frequency (p-value < 0.001), particularly in patients who had previously achieved good seizure control with Keppra. This finding is compatible with the previous study by Chaluvadi S. and Tharavichitkun J.[3,10] but contrasts with the other prior studies[7-9], as summarized in Table 5, and the guidelines from the Medicines and Healthcare Products Regulatory Agency (MHRA)[6], which classifies levetiracetam as category 3, suggesting that brand substitution is considered safe. The observed discrepancies in the efficacy of Letta, a formulation manufactured in Thailand, highlight the need for further investigation into its bioequivalence and potential variations in production, transportation, and storage practices at the hospital.

Table 5: Comparison of eight studies that switched antiepileptic drugs from original to generic levetiracetam, including this study.

Studies	Trimboli M	Lee GH	Contin M	Fanella M	Chaluvadi S	Tiamkao S	Tharavichitkun J	This study
Population	125	148	147	36	260	210	75	191
Levetiracetam monotherapy	47%	45.3%	-	-	35.5%	32.86%	22.7%	48.69%
Polytherapy	53%	54.7%	-	-	64.5%	67.14%	77.3%	51.31%
Switch back rate	None	4.8%	-	8%	42.9%	0.95%	-	2.09%
Side effects	Not difference	Not difference	-	8.33%	3.3%	3.81%	-	8.38%
Levetiracetam level	-	-	Not difference	Not difference	-	-	-	-
Median daily dosage of original levetiracetam	-	1,000 mg/day	-	-	-	1,000 mg/day	1,500 mg/day	1,000 mg/day
Median daily dosage of generic levetiracetam	-	1,000 mg/day	-	-	-	1,000 mg/day	1,500 mg/day	1,750 mg/day
Therapeutic equivalence	Not difference	Not difference	-	-	Difference, increased seizures on generic	Not difference	Similar seizure frequency but increased in the group with prior well-controlled seizures	Difference in the group with prior well-controlled seizures

Based on these findings, it is recommended that clinicians exercise caution when switching anticonvulsant formulations in patients with well-controlled seizures on the original formulation. Patients should be informed of the potential risks, including increased seizure frequency and other adverse effects. However, in patients who experienced an increase in seizure frequency but did not revert to Keppra, seizure control was successfully restored through dosage adjustments or the addition of other anticonvulsants. Adverse events were reported in 8.38% of patients, with no life-threatening occurrences.

In contrast, no significant difference in seizure control was observed in patients who had experienced more than one seizure per month prior to the switch to Letta. This may be due to the small sample size or the possibility that these patients have drug-resistant epilepsy, for which alternative therapeutic approaches, such as surgical intervention, may be necessary.

The limitations of this study include its retrospective design, which prevents the control of factors such as patient compliance and precipitating causes that may influence seizure occurrence. Furthermore, levetiracetam levels were not measured, limiting the ability to evaluate changes in drug concentration.

Conclusion

While the majority of patients maintained seizure control after switching from Keppra to the generic formulation Letta, a significant increase in seizure frequency was observed in those who had previously achieved stable seizure control. This suggests a potential difference in efficacy between the two formulations. Seizure control was restored in most cases through dosage adjustments or the addition of adjunct anticonvulsants. Patients with uncontrolled seizure did not show a significant change in seizure frequency following the switch, indicating that levetiracetam may not be effective for this subgroup. These findings emphasize the need for caution when switching anticonvulsants in patients with well-controlled seizures. Clinicians should consider alternative treatment options, including adjunct therapies or reversion to the original formulation, for patients who experience inadequate seizure control or adverse effects.

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