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Brand-to-generic Levetiracetam Switch in Patients with Epilepsy: Seizure Control and its Predictors in a Real-world Setting

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Abstract

BACKGROUND: Epilepsy is a common neurological disease. Treatment with original antiepileptic drugs may result in high cost. Levetiracetam (LEV) is a broad-spectrum antiepileptic drug. Several studies showed that generic LEV is safe, effective, and saves cost. There are limited data on predictors of seizure control in persons with epilepsy treated with LEV, particularly switch therapy to generic LEV.

METHODS: This study was a comparison study conducted at two tertiary care hospitals. One hospital used an original LEV, while another one switched to generic LEV. The outcomes of the study included seizure control after switching to generic LEV treatment, treatment cost, dosage of LEV, adverse events of LEV, switching therapy to original LEV, emergency room visit, and abnormal laboratory tests. These outcomes were compared between the generic and original LEV. Seizure control defined by free of seizure after switch therapy. Predictors of seizure control were analyzed by multiple logistic regression analysis.

RESULTS: During the study period, there were 96 eligible patients and treated with generic LEV in 61 patients (63.54%). Regarding treatment outcomes, the generic LEV group had significantly higher proportions of seizure control (91.80% vs. 45.71%) than the original LEV group. The original LEV group had significantly higher cost than the generic LEV group (65,250 vs. 9500 Baht; $p < 0.001$). The final model had two factors remaining: Generic LEV and frequency of seizure before switch therapy. Generic LEV was independently associated with seizure control with adjusted OR of 6.35 (95% CI of 1.73, 23.34).

CONCLUSION: Switch therapy to generic LEV is an alternative therapy with comparable efficacy, lower cost, and safe. Generic LEV and frequency of seizure attack before switch therapy to generic LEV may be related to seizure control.

Introduction

Epilepsy is a common neurological disease. Its incidence was 61.4 per 100,000 person-year but was high as 139.0 per 100,000 person-year in low-/middle-income countries [1]. It was estimated that epilepsy had a burden of over 13 million disability-adjusted life-years and standardized mortality ratio of 19.8 in low-/middle-income countries. Antiepileptic drug is a key factor for seizure control in persons with epilepsy. Levetiracetam (LEV) is a broad-spectrum antiepileptic drug with fewer side effects than older drugs, well tolerated, and approved for various seizure types [2], [3]. A previous study found that LEV had a long-term efficacy at 6 months for primary generalized seizures of 56.2% with minor side effects [4].

Original or brand LEV is effective, but may have high cost. As previously reported, using generic drug reduced expenditure of 84.3 billion USD [5]. The previous studies have shown that generic LEV is effective and safe compared with branded LEV as well as quality of life and bioequivalent [6], [7], [8], [9], [10]. Numbers of seizure attacks/month between those who treated with original LEV and generic LEV were equal at 0.7 times/month [7]. Regarding adverse effect, the original LEV had slightly higher percentages than generic LEV (27% vs. 24%). Even though several studies found that generic LEV is comparable with original LEV, there are limited data on predictors of seizure control in persons with epilepsy treated with LEV, particularly switch therapy to generic LEV.

Methods

This study was a comparison study conducted at two tertiary care hospitals. The inclusion criteria were persons with epilepsy aged of 15 years or over who received LEV treatment for at least 24 weeks. Those who were pregnant or did not have clinical data were excluded from the study. The study sites were university hospital and

provincial hospital. One hospital used an original LEV, while another one switched to generic LEV as study drug with the same dose of original LEV. Generic LEV is a 500 mg of LEV by MacroPhar Co. Ltd., Bangkok, Thailand, while original LEV is a 500 mg of LEV or Keppra manufactured by GlaxoSmithKline (Thailand) Ltd. The study period was between November 2020 and February 2021.

Medical records of eligible patients were reviewed before and after treatment with LEV. Clinical factors were studied including baseline characteristics, epilepsy duration, types of seizures, etiology of epilepsy, antiepileptic drug treatment, comorbid diseases, history of status epilepticus, history of seizure-related injury, and frequency of seizure attacks before LEV switch therapy.

The outcomes of the study included seizure control after switching to generic LEV treatment, treatment cost, dosage of LEV, adverse events of LEV, switching therapy to original LEV, emergency room visit, and abnormal laboratory tests. These outcomes were compared between the generic and original LEV. Seizure control defined by free of seizure after switch therapy, while treatment cost indicated cost from LEV treatment per year on the required dosage. Those who received generic LEV and unable to control seizures or presence of LEV side effect were an indication for switching therapy to the original LEV. Adverse events from LEV were recorded from the medical records.

Statistical analyses

Patients were categorized into two groups by LEV treatment arm: Generic and original LEV. Clinical factors and outcomes between both groups were compared by descriptive statistics. Factors associated with seizure control were computed using logistic regression analysis. A univariate logistic regression analysis was performed to find potential predictors for seizure control. Those potential factors were put in the multiple logistic regression analysis: Stepwise method. Factors with $p < 0.20$ by univariate logistic analysis were allowed to enter the final model, while factors with $p < 0.25$ were allowed to retain in the final model. Results were reported as crude odds ratio (OR) with 95% confidence interval (CI). Goodness-of-fit of the final predictive model was tested by Hosmer-Lemeshow test. Statistical analyses were performed by STATA software (College Station, Texas, USA).

Results

During the study period, there were 96 eligible patients and treated with generic LEV in 61 patients (63.54%). Age and sex were comparable between those treated with generic and original LEV (42.43 vs. 43.00 years and male 41.67% vs. 42.62%), as shown in Table 1. The generic LEV group had significant higher proportions of patients with dyslipidemia (21.31% vs. 5.71%) and frequency of seizure in 4 weeks before study participation (90.16% vs. 34.29%) than the original LEV group (Table 1). The original LEV group had significant longer epilepsy duration, more patients with partial seizures, post-traumatic brain injury, encephalitis, treated with other antiepileptic drug (phenytoin, sodium valproate, and phenobarbital), and history of seizures-related injury than the generic LEV group (Table 1).

Table 1: Characteristic of persons with epilepsy treated with generic LEV and original LEV

Characteristic	Total (n = 96)	Generic LEV (n = 61)	Original LEV (n = 35)	p
Male sex	40 (41.67)	26 (42.62)	14 (40.00)	0.802
Age: Mean ± SD; years	42.43 ± 18.75	43.00 ± 19.83	41.43 ± 16.94	0.323
Duration of disease: Median (min: max)	7 (0.33:47)	6 (0.33:43)	9 (0.33:47)	0.043
Type of seizures (n = 95); n (%)				
Partial seizures	57 (60.00)	28 (45.90)	29 (85.29)	<0.001
Generalized seizures	38 (40.00)	33 (54.10)	5 (14.71)	
Etiology of epilepsy				<0.001
Post-traumatic brain injury	7 (7.29)	2 (3.28)	5 (14.29)	
Post-craniotomy/craniectomy	4 (4.17)	2 (3.28)	2 (5.71)	
Encephalitis	5 (5.21)	1 (1.64)	4 (11.43)	
Meningitis	0 (0.00)	0 (0.00)	0 (0.00)	
Cysticercosis	0 (0.00)	0 (0.00)	0 (0.00)	
Calcification	0 (0.00)	0 (0.00)	0 (0.00)	
Hypoxic ischemic encephalopathy/post-cardiac arrest	1 (1.04)	1 (1.64)	0 (0.00)	
Hippocampal sclerosis	21 (21.00)	11 (13.30)	10 (7.70)	
Congenital disease	3 (3.13)	0 (0.00)	3 (8.57)	
Post-stroke seizures	18 (18.75)	11 (18.03)	7 (20.00)	
Encephalomalacia	2 (2.08)	0 (0.00)	2 (5.71)	
Dementia	0 (0.00)	0 (0.00)	0 (0.00)	
Others	35 (35.00)	33 (22.20)	2 (12.80)	
Other antiepileptic drug used during study period	62 (64.58)	31 (50.82)	31 (88.57)	<0.001
Phenytoin	16 (16.67)	5 (8.20)	11 (31.43)	0.003
Carbamazepine	11 (11.46)	5 (8.20)	6 (17.14)	0.201
Sodium valproate	36 (37.5)	18 (29.51)	18 (51.43)	0.033
Phenobarbital	10 (10.42)	3 (4.92)	7 (20.00)	0.034
Topiramate	12 (12.50)	6 (9.84)	6 (17.14)	0.345
Gabapentin	2 (2.08)	2 (3.28)	0 (0.00)	0.532
Lacosamide	1 (1.04)	0 (0.00)	1 (2.86)	0.365
Clonazepam	6 (6.25)	3 (4.92)	3 (8.57)	0.665
Other antiepileptic drugs	1 (1.04)	1 (1.64)	0 (0.00)	0.999
Comorbidity; n (%)	44 (45.83)	33 (54.10)	11 (31.43)	0.032
Diabetes mellitus	11 (11.46)	9 (14.75)	2 (5.71)	0.318
Hypertension	14 (14.58)	9 (14.75)	5 (14.29)	0.950
Dyslipidemia	15 (15.63)	13 (21.31)	2 (5.71)	0.043
Coronary heart disease	1 (1.04)	0 (0.00)	1 (2.86)	0.365
Chronic kidney disease	4 (4.17)	1 (1.64)	3 (8.57)	0.136
Chronic liver disease	3 (3.13)	1 (1.64)	2 (5.71)	0.552
Asthma	1 (1.04)	1 (1.64)	0 (0.00)	0.999
Hepatitis	2 (2.08)	1 (1.64)	1 (2.86)	0.999
Others	26 (27.08)	25 (40.98)	1 (2.86)	<0.001
History of status epilepticus	2 (2.08)	1 (1.64)	1 (2.86)	
History of seizure-related injury	8 (8.33)	2 (3.28)	6 (17.14)	0.048
Drive a car/motorcycle	4 (4.17)	2 (3.28)	2 (5.71)	0.621
History of traffic accident	1 (1.04)	0 (0.00)	1 (2.86)	0.365
Frequency of seizures per 4 weeks (prior study period), times				<0.001
0–3	67 (69.79)	55 (90.16)	12 (34.29)	
4–7	24 (25.00)	5 (8.20)	19 (54.29)	
> 8	5 (5.21)	1 (1.64)	4 (11.43)	

Data presented as number (%) unless indicated otherwise. LEV: Levetiracetam.

Regarding treatment outcomes, the generic LEV group had significantly higher proportions of seizure control (91.80% vs. 45.71%) than the original LEV group (Table 2). The original LEV group had significantly higher cost than the generic LEV group (65,250 vs. 9500 Baht; $p < 0.001$). The final model had two factors remaining: Generic LEV and frequency of seizure before switch therapy (Table 3). Generic LEV was independently associated with seizure control with adjusted OR of 6.35 (95% CI of 1.73, 23.34), while frequency of seizure before switch therapy of 8–12 times/4 weeks had adjusted OR of 15.97 (95% CI

Table 2: Treatment outcomes of persons with epilepsy treated with generic levetiracetam (LEV) and original LEV

Outcome	Total (n = 96)	Generic LEV (n = 61)	Original LEV (n = 35)	p
Seizure control	72 (75.00)	56 (91.80)	16 (45.71)	<0.001
Cost: Median (min: max); Baht/year	19,000 (4.350:152.250)	9500 (4.750:47.500)	65,250 (4.350:152.250)	<0.001
Dosage: Median (min: max); mg/day	1000 (100:5.000)	1000 (500:5.000)	1500 (100:3.500)	0.111
Adverse events of treatment	2 (2.08)	1 (1.64)	1 (2.86)	0.999
Do patient switching back to original LEV	0 (0.00)	0 (0.00)	0 (0.00)	-
Emergency room visit	6 (6.25)	2 (3.28)	4 (11.43)	0.186
Laboratory abnormality	2 (2.08)	0 (0.00)	2 (5.71)	0.130

Data presented as number (%) unless indicated otherwise. LEV: Levetiracetam.

of 1.31, 194.25). Hosmer-Lemeshow Chi-square of the final model was 5.91 (p = 0.052).

Table 3: Factors correlated with seizure control by multiple logistic regression analysis in persons with epilepsy treated with generic and original LEV

Factor	Crude OR (95% CI)	Adj OR (95% CI)
Frequency of seizure before switch therapy, times/4 weeks		
4–7	3.38 (0.32, 34.91)	3.99 (0.32, 49.04)
>8	34.28 (3.34, 351.30)	15.97 (1.31, 194.25)
Generic LEV	13.30 (4.29, 41.21)	6.35 (1.73, 23.34)

OR: Odds ratio; Adj: Adjusted, CI: Confidence interval; factors entered the stepwise multivariate logistic regression analysis included age, sex, duration of epilepsy, type of seizure, comorbidity, and duration of epilepsy. LEV: Levetiracetam.

Discussion

After switch therapy to generic LEV, the generic LEV group had significantly higher seizure controlled rate than original LEV. There was no statistically significant in terms of dosage, adverse events, emergency room visit, or laboratory abnormality (Table 3). None of 61 patients received generic LEV required switch back therapy to original LEV. Not surprisingly, another advantage of generic LEV is lower cost than original LEV by 6.86 times/year (Table 3).

Even though several studies reported comparable efficacy of generic and original LEV in switch therapy trials [9], [11], [12], this study found that generic LEV was a predictor of seizure controlled compared with original LEV. Note that the model was adjusted for baseline characteristics including age, sex, seizure type, presence of comorbidity, combined antiepileptic treatment, and frequency of seizure attack before switch therapy (Table 3). This statistical method can solve different baseline characteristics between the generic and original LEV group, as shown in Table 1.

In general, generic LEV has been reported to be safe, effective, and equal to original LEV in terms of bioequivalent. This study found that generic LEV may be associated with good seizure control compared with original LEV by 5.23 times (Table 3). The mechanism of these findings remains unclear. However, the study from Korea also found that generic LEV was associated with decreased seizure frequency after generic LEV switch therapy by 6.76%: 10 patients out of 148 patients [6]. In addition, those patients with decreased seizure with generic LEV also had more seizure attack before switch therapy as in this study [6]. That study also found that a median age was relatively younger in those with decreased seizure group than other groups but by descriptive statistics. In this study, several factors including age were put in the model but it was not retained in the final model. We believe that this statistical method: Logistic regression analysis is more robust and able to control for confounding factors than descriptive statistics in the previous study (shown at note of Table 3). However, further studies may be required to confirm the results of this study. In addition, no switch back therapy or serious side effects of generic LEV in this study as previously reported [13]. Note that the seizure control definition in this study was free of seizure attack.

There are some limitations in this study. First, the follow-up period was 4 months which was somewhat lower than the previous study at 6 months [6]. Second, some studies reported switch back or breakthrough seizure [8], [14], [15]. However, these three studies reported with four patients or 260 patients with 3 months follow-up. Finally, patient compliance was not studied as well as there are several epilepsy types and causes were included resulting in different in seizure control. Further studies are needed to evaluate these factors.

Conclusion

Switch therapy to generic LEV is an alternative therapy with comparable efficacy, lower cost, and safe. Generic LEV and frequency of seizure attack before switch therapy to generic LEV may be related to seizure control.

Ethical Statement

The ethical approval was obtained from the research ethics committee of Khon Kaen University, under number HE621121.

Data Availability Statement

All data relevant to the study are included in the article.

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