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Brand name to generic substitution of levetiracetam in patients with epilepsy

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ABSTRACT

Purpose: Levetiracetam is one of the most widely used antiepileptic drugs, but the evidence related to the safety of substitution from brand name to generic levetiracetam is scarce. The present study evaluated the risk of increased frequency of seizures after replacement of a brand-name levetiracetam with a generic product.
Methods: We enrolled patients with epilepsy who were treated with branded levetiracetam for at least 6 months of sustained use. Patients were advised to switch to the generic levetiracetam. We analyzed data from 6 months before, to 6 months after, generic substitution. Increased seizure frequency was defined as a≥ 50% increase in seizure frequency after conversion date compared with seizure frequency before the conversion date. We analyzed changes in seizure frequency and performed subgroup analysis according to changes in seizure frequency.
Results: We analyzed 148 epilepsy patients. Among the 148 patients, 109 (73.6%) were seizure-free before substitution and 105 patients remained seizure-free after switching. After generic substitution, an increased seizure frequency was noted in seven patients (4.7%), and a decreased seizure frequency was noted in 10 (6.8%). Patients with decreased seizure frequency were significantly younger ($p = 0.035$) than those with an unchanged seizure frequency.
Conclusion: This study suggests that the risk of increased seizure frequency after generic substitution was minimal. The generic substitution of levetiracetam was generally safe, although larger prospective studies are warranted to corroborate our findings.

1. Introduction

Generic formulations of antiepileptic drugs (AEDs) are currently available. These products have the same active pharmaceutical ingredients as those in branded products [1]. The bioequivalence of generic products is approved if the area under the drug plasma concentration-time curve (AUC) and maximum plasma drug concentration (Cmax) ratios of both products fall within 80–125% with 90% confidence intervals (CIs) [2]. Clinical evidence suggests that the differences between most branded and generic drugs are negligible [3]. The use of generic AEDs substantially reduces treatment cost and plays an important role in patient adherence due to the considerably lower price compared to branded products [4–8]. The American Epilepsy Society informed that drug substitution with FDA-approved generic products can reduce cost without compromising efficacy [9].

Nevertheless, controversy exists regarding the safety of generic substitution of AEDs [10–14]. The therapeutic dose of AEDs varies across patients and AEDs have numerous pharmacokinetic factors that may increase the probability of associated complications. Indeed, even small changes in AED plasma concentrations can elicit a breakthrough seizure [14–17]. Due to these issues, it is recommended that generic substitution is approved by an epilepsy medical specialist [18].

Levetiracetam (LEV, brand name Keppra; UCB S.A. Belgium) is a newer broad-spectrum AED and one of the most widely used AEDs that is approved for the treatment of focal and generalized epilepsy [19]. In November 2008, a generic competitor of Keppra was approved and released into the market [20]. Many studies that analyzed the substitution from brand name to generic AEDs included patients taking various AEDs. However, the evidence related specifically to the safety of substitution from brand-name to generic LEV is scarce [21–23]. Due to hospital policy changes, we were required to substitute brand-name LEV with a generic product produced by Dong-A pharmaceutical-Seoul, Korea. The situation was explained to patients, who agreed to change their prescriptions. Patients who disagreed with generic substitution were prescribed brand-name LEV at other hospitals. Patients used the same formulation, dose per tablet, and daily dose of LEV. Concomitant medications remained unchanged. We conducted a retrospective study aimed at assessing the risk of increased seizure frequency after

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replacement of a brand-name LEV with a generic product.

2. Methods

2.1. Subjects

Patients aged at least 16 years with epilepsy who were treated with LEV between March and September 2015 were enrolled in this study. They were recruited from the tertiary outpatient epilepsy clinic at the Department of Neurology, Pusan National University Hospital, Republic of Korea. Patients were included if they had converted from brand to generic LEV, had 6 or more months of sustained LEV use, had been receiving the same dose of AED including LEV for at least 6 months prior to generic substitution, and if their epilepsy duration was at least 1 year. Subjects were excluded if they had severe medical and psychiatric disorders and/or if their seizure frequency could not be quantified. All of the patients included in the study were regularly monitored by one of two physicians, both co-authors of this study. This study was approved by the Institutional Review Board of Pusan National University Hospital.

2.2. Assessment

A standardized data form was developed, and data were obtained retrospectively from individual patient medical records. Variables included in the database were age, sex, age at onset, classification of epilepsy, number and dose of concomitant administered AEDs, the dose of LEV, seizure frequency, magnetic resonance imaging (MRI) results, and electroencephalographic findings. Epilepsy was classified using the International League Against Epilepsy classification [24].

We analyzed data from 6 months before, to 6 months after substitution. The interval between visits was typically 3 months. The first date a patient received a prescription for generic LEV was considered their conversion date. Seizure frequency was reported by the patients and their family members. Seizure frequency was determined by seizure number during the 6 months before and after conversion date. Seizure freedom was defined by a seizure-free status during the 6 months before and after conversion date, respectively. An increased frequency of seizures was defined as a $\geq$ 50% increase in seizure frequency after conversion date from the seizure frequency before conversion date. We also registered potential adverse events.

2.3. Statistical analysis

Statistical analysis was performed using SPSS 22.0 (IBN corp., Armonk, NY, USA). Quantitative variables are expressed as the median with interquartile range (IQR) due to the non-parametric distribution. Qualitative variables were characterized by numbers and percentages. Wilcoxon signed-rank test was used to examine the difference between medians of seizure frequency before and after generic substitution. Chi-squared test (or Fisher exact test, where appropriate) and Kruskal-Wallis H test were used to assess the significance of the differences between subgroups according to changes in seizure frequency. Bonferroni's correction was applied to the post hoc analysis of between-group or within-group comparisons. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics (Table 1)

Between March and September 2015, 239 patients with epilepsy received at least one prescription for LEV. Of this group, 154 epilepsy patients met the inclusion criteria, but six patients were lost to follow-up. A total of 148 subjects was included in the final study cohort. Patients involved in this study had idiopathic epilepsy (10 patients, 6.8%), cryptogenic epilepsy (64 patients, 43.2%), or symptomatic epilepsy (74 patients, 50%). The median seizure frequency of all seizure types before conversion date was 0 (IQR 0–1) for 6 months. Sixty-six patients (44.6%) were on branded-LEV as monotherapy, and 82 patients (55.4%) as polytherapy in association with one or more other AEDs. The median LEV dose was 1000 mg/day.

Table 1
Clinical characteristics of the 148 patients.

Total number of patients (n)	148
Gender (male/female) n (%)	75 (50.7)/73 (49.3)
Age (years), median (IQR)	46.0 (28.3–61.0)
Onset age (years), median (IQR)	25.5 (14.3–52.0)
Duration of disease (years), median (IQR)	6.5 (2.0–18.0)
Dose of LEV (mg), median (IQR)	1000 (750-1000)
Number of other AEDs, median (IQR)	1.0 (0-2)
No concomitant AED, n (%)	67 (45.3)
1 concomitant AED, n (%)	40 (27.0)
2 concomitant AEDs, n (%)	24 (16.2)
$\geq$ 3 concomitant AEDs, n (%)	17 (11.5)
Seizure frequency at baseline (n/6 months), median (IQR)	0 (0–1)
Type of epilepsy, n (%)	
Focal	121 (81.8)
Generalized	14 (9.5)
Combined generalized & focal	3 (2.0)
Unknown	10 (6.8)

3.2. Seizure freedom

Initially, 109 patients (73.6%) were seizure-free during the 6 months before generic substitution. Seizure freedom was maintained in 105 patients (96.3%) and seizures occurred in four patients (3.7%) during the 6 months after substitution. Of the 39 patients who initially had seizures before substitution, eight patients were seizure-free after generic substitution. Finally, 113 patients (76.4%) were seizure-free at 6 months after substitution (Fig. 1).

3.3. Changes in seizure frequency

The baseline median frequency of all seizure types before conversion date was 0 (IQR 0–1) for 6 months. The median seizure frequency after substitution was the same as frequency before substitution (0 for 6 months, IQR 0–1). The difference between median seizure frequency associated with the original and generic brands was not significant ($P = 0.886$).

Of 66 patients with LEV as monotherapy, only one patient (1.5%) had an increased seizure frequency ($\geq$50% of the baseline frequency) and two patients (3.0%) had a decreased seizure frequency ($\leq$50% of the baseline frequency). Of 82 patients with LEV as polytherapy, six patients had an increased seizure frequency and eight patients had a decreased seizure frequency. Overall, the increased frequency of seizures was noted in seven patients (4.7%) during the 6 months after substitution. The dose of the generic LEV was increased in four patients. The other three patients had a breakthrough seizure without taking AEDs and were instructed to take medication regularly. Ten patients had a decreased seizure frequency (6.8%) (Fig. 2).

3.4. Characteristics of subgroups according to changes in seizure frequency (Table 2)

The subgroup that experienced increased seizure frequency comprised three men and four women. Six patients had focal epilepsy and one patient had generalized epilepsy. One patient was treated with LEV monotherapy, three with LEV and other AEDs, and three with LEV and more than two other AEDs. Medications used in polytherapy included lamotrigine (n = 3), carbamazepine (n = 3), valproate (n = 2), and topiramate (n = 1) .