Brand-to-Generic Levetiracetam Switch in Patients with Epilepsy in a Routine Clinical Setting

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Running title: Levetiracetam brand to generic switch

Key words: antiepileptic drug, generic drug substitution, Keppra, pharmacokinetics, bioequivalence, clinical practice

Number of text pages: 16

Number of words: 2882

Number of references: 38

Number of Figures: 1

Number of Tables: 3

Summary

Background: The therapeutic equivalence of generic and brand antiepileptic drugs, based on studies performed on healthy volunteers, has been questioned. We compare, in a routine clinical setting, brand versus generic levetiracetam (LEV) bioequivalence in patients with epilepsy and also the clinical efficacy and tolerability of the substitution.

Methods: A prospective, open-label, non-randomized, steady-state, multiple-dose, bioequivalence study was conducted in 12 patients with epilepsy (5 females), with a mean age of 38.4±16.2 years. Patients treated with the brand LEV (Keppra; UCB Pharma) were closely followed for a four-week period and subsequently switched to a generic LEV (Pharmaten) and followed for another four-week period. Blood samples were collected at the end of each 4-week period, during a dose interval for each formulation, for LEV concentration measurements by liquid chromatography mass spectrometry. Steady-state area under the curve (AUC) and peak plasma concentration (Cmax) data were subjected to conventional average bioequivalence analysis. Secondary clinical outcomes, including seizure frequency and adverse events, were recorded.

Results: Patients had epilepsy for a mean period of 14.1±10.6 years and the mean daily LEV dose was 2583.3±763.7 mg. The mean AUC±SD and Cmax±SD was 288.4±86.3 (mg/L) h and 37.8±10.4 mg/L respectively for brand LEV and 319.2±104.7 (mg/L) h and 41.6±12.3 mg/L respectively for the generic LEV. Statistic analysis showed no statistical significant difference in bioequivalence. Also, no change in seizures frequency and/or adverse events was recorded.

Conclusions: In our clinical setting, generic LEV was determined to be bioequivalent to brand LEV. Furthermore, seizures frequency or/and adverse events were not affected upon switching from brand to generic LEV.

Introduction

Brand versus generic medications is a topic of debate and discussion, with most national governments encouraging the use of generic medicines and many healthcare systems supporting policies of substituting brand original drugs with generic drugs, mainly for cost saving reasons[1]. This can be particularly important for patients with limited income and public insurance programs with constrained budgets.

Since 1984, manufacturers rely on pharmaceutical equivalence and bioequivalence (BE) of generic products to the original brand name drug for approval by the Food and Drug Administration (FDA), since it is not required to directly demonstrate the safety and efficacy of generic products in clinical trials[2]. Such studies generally evaluate the ratio of the generic product's area under the curve plasma concentration (AUC) versus the brand-name product's AUC and the ratio of the generic product's maximum concentration (Cmax) to the brand-name product's Cmax[3], in young healthy male volunteers. The FDA definition of bioequivalence requires that the 90% confidence intervals for the ratio of brand-to-generic AUC and Cmax fall within an acceptance interval of 0.80–1.25 (known as the "-20%/+25% rule")[4]. Because of these approval requirements[5, 6], generics are considered by some physicians and patients to be more problematic than brand-name medications. Indeed generic substitution has become an emotional issue among physicians and patients.

Of particular concern is whether patients prescribed generics may be at increased risk of therapeutic failure and/or side-effects[7, 8], if small potential difference in BE variability occur[9, 10], as with AEDs with low bioavailability and solubility[9] or with AEDs with a narrow therapeutic index[10, 11]. Furthermore studies have shown switchback rates for AEDs are substantially higher than for non-AEDs[10, 12]. Loss of seizure control can have substantial medical, financial, and social consequences for patients with epilepsy, particularly those that are seizure-free on a particular branded AED.

The issue of the interchangeability of brand and generic AEDs has increased recently because many clinically useful second generation AEDs have reached the end of their patent protection and various generic versions have been approved[13].

In the present study, steady-state AUC and Cmax values were subjected to conventional average bioequivalence analysis (ABE) in patients with epilepsy, switched from brand levetiracetam (LEV) to generic LEV in a routine clinical practice setting. Secondary clinical outcomes, including seizure frequency and adverse events, were also recorded to determine the clinical efficacy and tolerability of the substitution.

Methods

Study design

A prospective, open-label, non-randomized, steady-state, multiple-dose, bioequivalence study was conducted in patients with epilepsy, to compare brand (Keppra; UCB Pharma; Belgium) versus generic LEV (Pharmaten; Greece). The chosen generic is the most commonly prescribed LEV generic in Greece.

Study population

Subjects were adult patients treated with brand LEV for focal epilepsy. They were recruited from consecutive epilepsy patients attending the Outpatient Epilepsy Clinics at the University Hospital of Ioannina and at the Evagelismos Hospital, Athens, Greece, during 8 months (June 2014 to January 2015). To be eligible for the study, patients were being prescribed Keppra LEV during the previous 2 months and were to be switched to a generic, as part of their routine clinical treatment. Because the formulation switch was part of the routine clinical management of patients, and therefore considered to be a non-interventional study, it was not necessary to obtain specific ethical approval. Instead, the Hospital Scientific Committee of both hospitals approved the study along with the patient consent protocol. The study protocol was in compliance with the Helsinki Declaration and informed consent was signed by all patients.

Patients treated with the brand LEV were closely followed for a four-week period during which seizure frequency and adverse effects were recorded and subsequently switched to a generic LEV and followed for further four-week period during which seizure frequency and adverse effects were again recorded. Blood samples were collected at the end of each 4-week period, during a dose interval for each formulation, for LEV concentration measurements by liquid

chromatography/mass spectrometry. Blood samples were collected at 5 minutes prior to LEV ingestion and at 1, 2, 4, 8 and 12 hours post LEV ingestion. Plasma samples were stored frozen at -24 ° C until analyzed for LEV content. Steady-state AUC and Cmax data were subjected to conventional ABE analysis. Secondary clinical outcomes, including seizure frequency and adverse events, were recorded.

Patients continued to take any concomitant AEDs and indeed drugs used to treat concomitant disorders. However, because adherence to their medications was essential, it was monitored by tablet counts and also by confirmation that LEV was ingested within 1 h of the scheduled dose time during the two previous days prior to pharmacokinetic sampling. Because our patients were being evaluated in a routine clinical setting, patients were neither fasting nor advised as to restrict any aspect of the normal diet or lifestyle.

LEV Analysis

LEV concentration analysis was undertaken by liquid chromatography/mass spectroscopy (LC/MS) using a fully validated methodology in routine use within the Therapeutic Drug Monitoring Unit at the Chalfont Centre for Epilepsy. Validation was based on the most recent versions of the guidelines on bionalytical method validation of the European Medicines Agency and the US Food and Drug Administration (EMA, 2013; FDA 3-13)[4, 5]. Briefly, an Agilent 1200 series automated LC with an Agilent 6400 series triple quad MS (Agilent Technologies, Stockport, Cheshire, UK) and a HiQ sil C18 column were used. Plasma (24 μL) were extracted with 500 μL acetonitrile and prepared for LC/MS analysis by use of a Gilson Quad-Z215 liquid handler (Gilson Instrumentation Services, Luton, Bedfordshire, UK). Calibration curve linearity was observed over the concentration range of 2-170 mg/L. The lower limit of quantification for LEV was 2.0 mg/L and the lowest limit of detection was 0.3 mg/L. The inter-assay and intra-assay coefficient of variation was 3.7-8.6% and 0.9-1.8% respectively. The measurement uncertainty for LEV was 5.8%.

Statistical analysis and pharmacokinetics and bioequivalence analysis

The continuous variables (e.g. age and weight) are presented as mean and standard deviation (SD), median, minimum and maximum values.

Shapiro-Wilk Normality Test was applied to the transformed AUC and Cmax differences between the brand and generic formulations; i.e. $Ln(X_{Generic}) - Ln(X_{Brand})$. The bioequivalence of the two formulations was tested according to the following parameters: AUC- trapezoidal rule, as an index of extent of absorption, and Cmax, as an index of rate of absorption. For these parameters the following hypotheses were tested: H_0: $\mu_{Generic}/\mu_{Brand} \leq 0.80$ or $\mu_{Generic}/\mu_{Brand} \geq 1.25$ (bio<u>in</u>equivalence) versus H_1: $0.80 < \mu_{Generic}/\mu_{Brand} < 1.25$ (bioequivalence) ($\alpha=0.05$ for each direction, where μGeneric is the true (population) mean of the corresponding parameter for the Generic product and μBrand is the true (population) mean of the corresponding parameter for the Brand product (original measurements).

The point estimate for the ratio $\mu_{Generic}/\mu_{Brand}$ was computed by the formula: $\mu_{Generic}/\mu_{Brand} = \exp(\text{mean}(Ln(X_{Generic})) - \text{mean}(Ln(X_{Brand})))$, while the 90% confidence interval (C.I.) for $\mu_{Generic}/\mu_{Brand}$ was computed using the following formula: C.I. = (e^L, e^U), where: $L = (\text{mean}(Ln(X_{Generic})) - \text{mean}(Ln(X_{Brand}))) - t(0.05, 14) \sqrt{(2s^2/N)}$ and $U = (\text{mean}(Ln(X_{Generic})) - \text{mean}(Ln(X_{Brand}))) + t(0.05, 14) \cdot \sqrt{(2s^2/N)}$. X_{Brand} and $X_{Generic}$ are the AUC or Cmax of brand and generic measurements respectively, s^2 is the variance of the corresponding Ln-differences between brand and generic product, that is $Ln(X_{Generic}) - Ln(X_{Brand})$, and $t(0.05, 14)$ is the 5% upper percentile of T distribution with 14 degrees of freedom. If the corresponding C.I. was within the acceptance limits (0.80, 1.25) the bioequivalence of the two products – regarding the respective parameter - was accepted. (Note: (L,U) is a 90% C.I. for the mean difference between the Ln-transformed generic and brand data).

The Wilcoxon signed rank test was used to compare Tmax values for brand and generic formulations. The t-test was used to compare the Liverpool Adverse Event Profile scoring between brand and generic formulations.

Outcome

The primary pharmacokinetic outcome was the bioequivalence of two key pharmacokinetic parameters (AUC and Cmax), between the brand and the generic LEV formulations. The secondary pharmacokinetic outcome was Tmax.

The secondary pharmacodynamic outcomes included changes in seizure frequency and/or adverse effects (AEs). Seizures were assessed from data captured

daily, by each patient, in a paper diary. AEs were based on self-reporting, by use of the Liverpool Adverse Events Profile; each AE was scored from 1-4, based on the absence (scored as 1) or the presence and the severity of AE (scored from 2-4)[14].

Results

Study Population

Twelve patients (5 females) were enrolled in the study during 8 months. Their mean ($\pm$ sd) age was 38.4$\pm$16.2 years and their mean ($\pm$ sd) weight was 82.3$\pm$16.4 kg.

Patients had epilepsy for a mean ($\pm$ sd) period of 14.1$\pm$10.6 years and the mean ($\pm$ sd) daily LEV dose was 2583.3$\pm$763.7 mg. Patient characteristics are summarized in Table 1.

Pharmacokinetic Properties - Bioequivalence

The mean plasma LEV AUC$\pm$SD was 288.4$\pm$86.3 (mg/L) h for brand LEV and 319.2$\pm$104.7 (mg/L) h for the generic formulation. AUC, Cmax and Tmax values for each individual patient are shown in Table 2. Figure 1 shows the mean ($\pm$SD) LEV plasma concentration versus time curves for the brand and generic LEV formulations.

The difference between the means of the Ln-transformed data $-$ mean $(Ln(X_{Generic}))$-mean$(Ln(X_{Brand}))$ - was 0.090 while the 90% C.I. for the same difference was (0.004, 0.175). Consequently, the point estimate of $\mu_{Generic}/\mu_{Brand}$ was 1.094 and the 90% C.I. for the same ratio was (1.004, 1.191) which laid within the acceptance limits of bioequivalence .

For Cmax, the mean$\pm$SD was 37.8$\pm$10.4 for brand LEV and 41.6$\pm$12.3 for the generic formulation. The difference between the means of the Ln-transformed data - mean$(Ln(X_{Generic}))$-mean$(Ln(X_{Brand}))$ - was 0.085 while the 90% C.I. for the same difference was: (-0.006, 0.178). Consequently, the point estimate of $\mu_{Generic}/\mu_{Brand}$ was 1.089 and the 90% C.I. for the same ratio is (0.993, 1.195) which laid within the acceptance limits for bioequivalence, with respect to Cmax .

The mean$\pm$SD of T_{max} was 1.3$\pm$0.4 h for the brand product and 1.1$\pm$0.3 h for the generic product. The median value was 1.0 for both products. No statistically

significant difference was detected between the two LEV formulations (Wilcoxon signed rank test p-value =0.25).

<u>Efficacy and tolerability</u>

During the 4-week LEV brand ingestion the average seizure number was 1.2, whilst the average seizures number during the 4-week LEV generic ingestion was 1.3. Seven patients reported the same number of seizures during the brand and the generic LEV periods (five of these patients had no seizures when ingesting the brand LEV; and this was the case during the generic LEV). Three patients had fewer seizures on the brand LEV (one of these patients had no seizures on the brand product and had one and two seizures on the generic product, accordingly), while two patients had less seizures on the generic product (one patient had one seizure on the brand product and no seizures on the generic product) (Table 3).

The AEs, during brand and generic dosing, were similar. Using the Liverpool Adverse Effect Profile Scoring, a sum of scores for the presence and severity of AEs, was calculated for both groups. The mean±SD of the brand product score was 33.6±14.2 while the score for the generic product was 33.8±10.2. No statistically significant difference was observed between the two products: t-test p-value=0.95 (Table 3).

Discussion

Generic AEDs are not considered to be inferior to branded AEDs as long as the same generic formulation is continued to be prescribed. Their unquestionable advantage is that they are substantially cheaper than the branded drug and this is of economic benefit to patients and health providers. However, there is substantial concern, often emotional, that generic drugs are not therapeutically equivalent to the branded versions. The concerns are that studies, typically single-dose studies in healthy male volunteers, do not represent the real-life setting in which generic substations would occur.

The evidence that generic AED substitution may be problematic is primarily based on patient surveys[15-18], physician survey[7, 18-20], studies of switch-back rates[10, 12, 21], studies of costs[10, 22, 23] and specific association studies[24]. The ideal comparison of a

brand and generic AED would be that of a randomized control trial in patients with epilepsy and two such studies involving lamotrigine have recently been published[25,26]. Both these studies provide strong evidence that, at least for lamotrigine, concerns about generic substitution are largely misplaced. The study of Ting et al (2015)[25] compared steady-state lamotrigine plasma concentrations in 34 generic-brittle patients (i.e. patients with a confirmed history of having potential problems with generic switching) and observed that adverse effects were not related to the small (but allowable) pharmacokinetic differences that occur between brand and generic formulations. The study of Privitera et al (2016)[26] comprised of 33 patients with epilepsy who underwent repeated switching between two lamotrigine generic products that were identified as having the lowest and highest bioavailability (compared to brand) sold in the USA. Not only were the two generic products determined to be bioequivalent but, in addition, there were no significant changes in seizure control or adverse effects.

The present prospective, open-label, non-randomized, steady-state, multi-dose, bioequivalence study, reflective of every day clinical practice and conducted in 12 patients with epilepsy, corroborate the studies of Ting et al (2015)[25] and Privitera et al (2016)[26] that concerns about generic substitution are largely misplaced. Our study population comprised both males and females and of various ages, various seizure frequency, on concomitant AEDs and various other non-AED drugs; characteristics typically encountered in a routine clinical setting. All patients underwent substitution of their branded LEV with that of a generic LEV formulation and based on bioequivalence criteria of AUC and Cmax values, the two formulations were considered to be bioequivalent (Figure 1). Furthermore, substitution was not associated with any significant change in seizure frequency or adverse affects severity p=0.95).

The physicochemical characteristics of a particular drug and whether or not it has a narrow therapeutic index would be expected to impact on bioequivalence and indeed there have been numerous such studies involving the older first generation AEDs - phenytoin, carbamazepine and valproic acid[27-33]. In these studies, brand and generic carbamazepine[30-33] and valproic acid[34] were determined to be bioequivalent whilst that of phenytoin, which has a narrow therapeutic index, was not[27-29]. For

carbamazepine, there was no significant difference in seizure frequency, nor in cognitive profile[35], although Hartley et al (1991) observed more adverse events during the generic ingestion[33].

Because the new second generations AEDs have a more favorable pharmacokinetic profile than that of the older first generation[36] they may be less prone to in-equivalence upon generic substitution and this is corroborated by our study. That a recent case report on 4 patients[37] reported an increased incidence of seizures when treatment was switched from brand to generic LEV does not confirm in-equivalence because plasma LEV concentrations were not measured prior to or after the brand to generic switch was made, nor were LEV concentrations measured prior to or after the switchback.

The limitations of this study are that although no significant difference in seizures frequency or adverse effects was observed, the sample size and baseline seizure frequency were not sufficiently powered to detect differences. Also, it is not known how many of the patients investigated were generic-brittle patients who might be particularly susceptible to experiencing adverse effects consequent to a formulation change. A further limitation is that the study design was open and non-randomised in design.

Conclusion

Patients and physicians have concerns that generic AEDs may not be bioequivalent to that of brand formulations and consequently generic drug substitution may cause therapeutic failure or increased risk of adverse effects. The present study of 12 patients with epilepsy, with characteristics typically encountered in a routine clinical setting, entailed substitution of their branded LEV with that of a generic LEV formulation and based on bioequivalence criteria the two formulations were concluded to be bioequivalent. Whether these data can be extrapolated to other AEDs is not known. However, as a rule of thumb when a planned generic substitution is to occur, it is important to measure blood concentrations before and after substitution so that if seizure breakthrough occurs or adverse effect presents, the contribution of in-equivalence can be more readily ascertained[38].

Disclosures:

We confirm that we have read the Journal's position on issues involved in ethical publications and affirm that this report is consistent with those guidelines.

PNP has received grant support from and has served as a paid consultant for UCB Pharma, the manufacturer of branded levetiracetam.

SM, DC, SG, AS, ES, AV, APK have no conflicts of interest to declare.

Pharmaten, the manufacturer of generic levetiracetam, paid for the statistical analysis to be undertaken by an independent statistician.

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Figure Legend

Figure 1: Mean (±SD) levetiracetam (LEV) plasma concentration versus time curves for brand (n=12) and generic (n = 12)LEV formulations
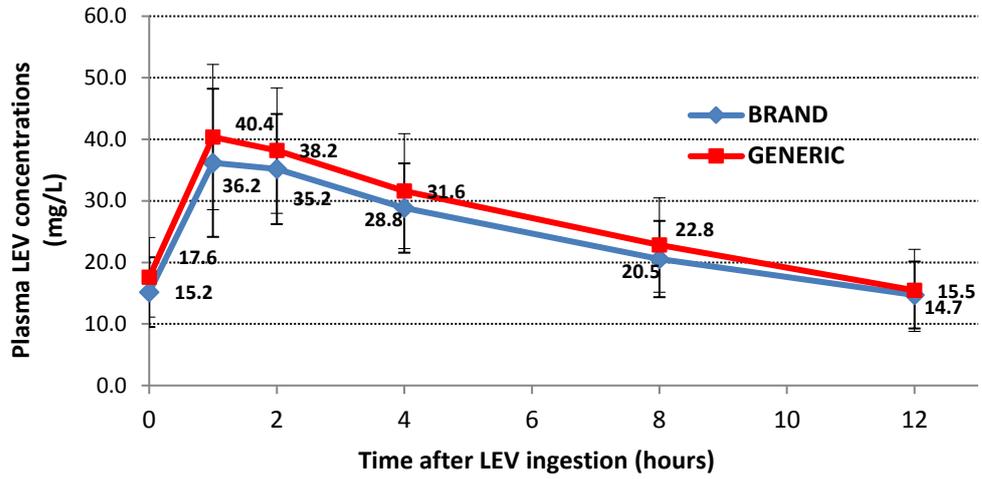
Table 1: Patient characteristics

Patient	Gender	Age (years)	Weight (kg)	LEV dose/day (mg)	Epilepsy duration (years)	Concomitant AEDs	Concomitant non-AEDs
1	Male	21	80.5	4000	5	Topiramate Lacosamide	0
2	Male	39	85	3000	20	Clonazepam Citalopram Oxcarbazepine	0
3	Male	47	97	3000	31	Carbamazepine Pregabalin	0
4	Male	29	98	3000	9	Carbamazepine Phenobarbital Topiramate	0
5	Female	29	63	1000	17	0	Ferrous sulphate
6	Male	22	77	3000	5	Lacosamide Oxcarbazepine	0
7	Female	48	53	2000	15	0	0
8	Female	37	80	2000	10	0	0
9	Male	79	70	2500	1	0	Aloperidin Omeprazole
10	Female	27	75	2500	15	Zonisamide	Ferrous sulphate
11	Male	32	105	3000	30	Oxcarbazepine Zonisamide	Bromazepam Ramipril
12	Female	51	105	2000	25	Clobazam Lacosamide Valproic acid	Thyrormone
Mean		38	82	2583	14	-	-
Median		34	80	2750	12	-	-
SD		16	16	764	11	-	-
Minimum		21	53	1000	1	0	0
Maximum		79	105	4000	31	3	2

AEDs = antiepileptic drugs; LEV = levetiracetam

Table 2: Pharmacokinetic parameters for brand and generic levetiracetam formulations

Patients	Brand			Generic		
	AUC (mg/L)h	C_{max} (mg/L)	T_{max}(h)	AUC (mg/L)h	C_{max}, (mg/L)	T_{max} (h)
1	377.0	45.0	2.0	423.2	55.0	1.0
2	263.7	32.0	2.0	294.2	47.0	1.0
3	276.0	30.0	1.0	300.5	33.0	1.0
4	261.0	43.0	1.0	370.0	42.0	1.0
5	147.2	20.0	1.0	124.4	16.0	1.0
6	196.0	33.0	1.0	234.6	41.0	1.0
7	398.7	56.0	1.0	427.9	62.0	1.0
8	297.5	43.0	1.0	293.4	40.0	1.0
9	435.0	46.0	2.0	526.6	55.0	2.0
10	195.0	24.0	1.0	276.0	32.0	1.0
11	327.8	45.0	1.0	299.4	40.0	1.0
12	286.2	36.0	2.0	260.5	36.0	1.0
Mean	288.4	37.8	1.3	319.2	41.6	1.1
Median	281.1	39.5	1.0	296.8	40.5	1.0
SD	86.3	10.4	0.5	104.7	12.3	0.4
Minimum	147.2	20.0	1.0	124.4	16.0	1.0
Maximum	435.0	56.0	2.0	526.6	62.0	2.0

Table 3: Seizures number and Liverpool Adverse Effect Profile (LAEP) for brand and generic levetiracetam formulations

Patient	Seizures number* Brand	Seizures number* Generic	LAEP Score Brand	LAEP Score Generic
1	4	1	19	19
2	0	0	38	39
3	0	2	26	23
4	0	0	32	44
5	0	0	23	39
6	2	4	22	23
7	0	0	33	39
8	0	0	70	52
9	1	0	30	30
10	2	3	51	40
11	2	2	28	34
12	4	4	31	23
Mean	1.2	1.3	33.6	33.8
Median	0.5	0.5	30.5	36.5
SD	1.5	1.6	14.2	10.2
Minimum	0	0	19	19
Maximum	4	4	70	52

* Number of seizures during a four week period