Seizure 48 (2017) 1–6

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Brand-to-generic levetiracetam switch in patients with epilepsy in a routine clinical setting

Sofia Markoula[a], Dimitrios Chatzistefanidis[a], Stylianos Gatzonis[b], Anna Siatouni[b], Eleftheria Siarava[a], Anastasia Verentzioti[b], Athanassios P Kyritsis[a], Philip N. Patsalos[c,d,*]

[a] University Hospital of Ioannina, Department of Neurology, Greece
[b] Medical School, National and Kapodistrian University of Athens, Greece
[c] NIHR University College London Hospitals Biomedical Research Centre, Department of Clinical & Experimental Epilepsy, UCL Institute of Neurology, London, UK
[d] Epilepsy Society, Chalfont Centre for Epilepsy, Chalfont St Peter, UK

ARTICLE INFO

Article history:
Received 17 January 2017
Accepted 18 March 2017
Available online xxx

Keywords:
Antiepileptic drug
Generic drug substitution
Keppra
Pharmacokinetics
Bioequivalence
Clinical practice

ABSTRACT

Purpose: 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.

1. 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

* Corresponding author at: Department of Clinical and Experimental Epilepsy, UCL- Institute of Neurology, Queen Square, London, WC1N 3BG, United Kingdom.
E-mail address: P.Patsalos@ucl.ac.uk (P.N. Patsalos).

http://dx.doi.org/10.1016/j.seizure.2017.03.012
1059-1311/

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.

2. Methods

2.1. 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.

2.2. 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.

2.3. 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%.

2.4. 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 $\mu_{Generic}/\mu_{Brand} \geq 1.25$ (bioinequivalence) 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 $U = (\text{mean}(Ln(X_{Generic})) - \text{mean}(Ln(X_{Brand}))) + t(0.05, 14).\sqrt{(2s^2/N)}$. 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%