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Impact of generic substitution on levetiracetam serum concentration—A prospective study in an outpatient setting

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ABSTRACT

Background: Switching patients from a branded antiepileptic drug (AED) to a generic is often challenging. Several studies have shown that considerable proportions of patients report deteriorated seizure control or increased adverse effects, enforcing a switchback to the original drug. Since tolerability and seizure control usually correlate with AED serum concentrations, we examined the fluctuation of levetiracetam (LEV) serum concentrations in patients with epilepsy before and after generic substitution.

Methods: This was an 18-week, naturalistic, open, prospective, two-center study. After a baseline period of 10 weeks, 33 outpatients on stable treatment with branded LEV (Keppra®) either continued with this product or were switched overnight to a generic LEV preparation (1A Pharma) for an eight-week study period. Throughout the study, patients were monitored with bi-weekly LEV serum concentration measurements and seizure diaries.

Results: 16 out of 33 patients were switched to a generic LEV product. No switchbacks were seen. LEV dose, LEV serum concentrations, fluctuation index and concentration/dose-ratio (C/D-ratio) were not significantly different within-group (baseline vs. study period) or between-group. Large within-subject variability in serum concentrations was seen in both groups. None of the patients that were seizure-free before inclusion experienced seizures while on the generic LEV product.

Conclusions: Our results show equal fluctuation of LEV serum concentrations with branded LEV and the generic LEV. Most importantly, within-subject variability was much larger than the small, non-significant differences between brands.

1. Introduction

In the European Union, LEV was approved under the brand name Keppra® in September 2000. Since the expiration of the patent, several generic LEV preparations have been marketed. Switching patients from a branded AED preparation to a generic one with the same active ingredient is often a challenging task. Several studies have shown that considerable proportions of patients report either a deterioration in seizure control or increased adverse effects, enforcing a switch back to the original preparation (Andermann et al., 2007; Chaluvadi et al., 2011; Fitzgerald and Jacobson, 2011). Both adverse effects and loss of seizure control often correlate with increased or decreased AED serum concentrations but they may also be related to psychological factors (Espay et al., 2015; Kesselheim et al., 2013).

Generic products must demonstrate bioequivalence (BE) in rate and extent of absorption, as indicated by peak plasma concentration (C_{max}) and area under the concentration-time-curve (AUC) to receive a marketing license. For ordinary BE studies, the FDA and other medical drug authorities require that the 90% confidence interval for the average test/reference-ratio of these criteria must fall within a range of 80–125% of the reference product (European Medicines Agency, 2010; Food and Drug Administration, 2002, 2013). These limits are based on the clinical judgment that a difference less than 20% is not clinically significant (Food and Drug Administration, 2001). It must be noted that this approach is based on average data, i.e. mean values (so-called *average BE*). Consequently, BE may be demonstrated even if BE criteria

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are not met in individual subjects. Other approaches to establish BE exist, e.g. the 75/75 rule or the 80/20 rule (Rasheed and Siddiqui, 2015), but they are not commonly used.

For drugs with a narrow therapeutic index (NTI), a smaller range of 90–111% plus a reference-scaled BE-approach (three- or four-period cross-over study, repeated switches between test and reference drug) and analysis of within-subject variability are often required (Yu et al., 2015). To date, two AEDs (carbamazepine and phenytoin) have been classified by the FDA as NTI drugs (Food and Drug Administration, 2014, 2015).

A review of 2070 BE-studies evaluated by the FDA in the period of 1996–2007 reported that the average differences between the generic product and the brand product in terms of C_{max} and AUC were as low as 4.35% and 3.56%. In almost 98% of these studies, the AUC of the generic drug differed less than 10% from the original product (Davit et al., 2009).

Once bioequivalence has been proven, increased adverse effects and deteriorated seizure control are not expected to be a common problem after generic substitution. However, conventional BE studies usually apply a single-dose design and are performed in young, healthy subjects. Moreover, standard BE studies are based on average values and do not address larger differences in individual subjects, even if they exceed 20 or 25%. Such large within-subject variability may however gain clinical relevance in the individual patient.

One possible explanation for the reported adverse outcome of generic substitution could therefore be that under everyday clinical conditions and over longer time, the generic product might exhibit larger fluctuations in serum concentrations, compared to the original product, at least in individual patients.

Our goal was therefore to examine the fluctuation of LEV steady-state serum concentrations in patients with epilepsy before and after a switch from branded LEV to a generic LEV product.

2. Methods

2.1. Study design

An outline of the study design is shown in Appendix A. This was a prospective, naturalistic, open, non-randomized cohort study carried out in two out-patient clinics in the southern part of Sweden (Skåne University Hospital in Lund, and Helsingborg General Hospital).

Study participants were monitored over a 10-week baseline period (covering six bi-weekly clinical visits from T-10 to T0). One group (KEP-KEP) then continued using Keppra® while the other group switched to a generic LEV product (KEP-LEV; Levetiracetam 1A Pharma®) using the same dosing schedule as before. After T0, patients were followed for another eight weeks (study period; four bi-weekly visits from T2 to T8). Drug-fasting blood samples were taken at T-10, T-8, T-6, T-4, T-2, T0, T2, T4, T6, and T8, and analyzed for LEV. Thus, each patient contributed with six LEV serum concentrations during baseline and four serum concentrations during the study period. The daily dose, time of last intake and time of blood sampling was recorded for each blood sample. The plasma half-life of LEV is 6–8 h in adults and up to 11 h in the elderly (Patsalos, 2004; Wright et al., 2013) and therefore the new pharmacokinetic steady state after the switch was assumed to be established after two days at the latest. Since the next clinical visit was scheduled 14 days after the switch, a separate wash-out period between baseline and study period was considered unnecessary.

This report focuses on pharmacokinetic data. However, seizure frequency was monitored. The first recording of seizure frequency was retrospective, based on the patients' own estimation of their average seizure frequency during the 12 months before enrolment. After enrolment, patients were asked to keep a seizure diary. The two following recordings (at T0 and T8) were based on this diary. Seizure frequency is presented as seizure days, i.e. days with at least one seizure regardless of seizure type. Results on other clinical outcome parameters like adverse events and quality of life will be published separately.

2.2. Patient selection

Patient inclusion started in May 2014 and ended in April 2016. Inclusion criteria: at least 18 years of age; on stable treatment with branded LEV (Keppra®) for at least four weeks prior to inclusion. Exclusion criteria were pregnancy or progressive structural etiology implying a risk for seizure augmentation during participation.

At routinely scheduled visits, patients on stable treatment with branded LEV (Keppra®) were evaluated by their treating neurologist whether they were eligible for a switch to generic LEV. They were then provisionally assigned to one of the two groups, either KEP-KEP or KEP-LEV, and subsequently asked for participation in the study. This implies that all generic switches were done voluntarily and with the patients' informed consent. Relevant demographic and clinical data were recorded at inclusion and continuously monitored during the study.

2.3. Analysis of levetiracetam

Levetiracetam in serum was analyzed by a LC–MS/MS (liquid chromatography mass spectrometry) method developed in our laboratory. Levetiracetam-d6 was used as internal standard and a calibration curve with quadratic fit and 1/x as weighting was applied. Samples were analyzed between June 14, 2014 and September 25, 2016. During this period, 258 quality control samples at 5.0 and 500 μmol/L were analyzed, with a CV% of 4.5 and 2.5%. The accuracy at both levels was 100.8%. The lower and upper limit of quantitation were 2.5 μmol/L and 640 μmol/L. Serum samples were analyzed consecutively as routine samples and the ordinary sampling procedures were followed. After blood was drawn, the samples were left standing at ambient temperature for 30 min before centrifugation (10 min at 2000*g*). The serum was transferred to a separate tube and sent to the laboratory. In the laboratory, samples were put in a refrigerator (+4 °C) until analysis. All samples were analyzed within a week from arrival at the laboratory.

2.4. Calculations and statistics

An *a-priori* power calculation (alpha = 0.05, beta = 0.2) based on 82 routine LEV serum concentration measurements resulted in a minimum sample size of 13 patients per group in order to detect a ≥20% difference in mean LEV serum concentrations.

Because LEV has a relatively short plasma half-life of about six to eight hours in adults (Patsalos, 2004), serum concentrations may be considerably affected by variations in the elapsed time between last intake and blood sampling. To eliminate this confounding factor, and since LEV exhibits linear pharmacokinetics, all LEV serum concentrations were standardized to a 12-h-value by using the following formula: $C_{12} = C_t \times e^{exp(-k(12-t))}$ where C_{12} = LEV serum concentration at 12 h after last intake; C_t = actual serum concentration measured at time t; e = Euler's number (2.72); k = elimination constant of LEV; t = number of hours between last dose and blood sampling. The elimination constant k was calculated by using the following formula: $k = ln2/t_{1/2}$ where $ln2 = 0.693$, and $t_{1/2} = 7$ h. These time-standardized serum concentrations were used for all following calculations as described below.

For between-group comparison of serum concentrations per treatment period (baseline period vs study period), all serum concentrations were first dose-normalized to 1500 mg. Because normality-testing indicated non-normal distribution, data were then log-transformed, and then the ratio of the geometric group means and the 90% confidence intervals of the differences were calculated.

The serum concentration/dose ratio (C/D-ratio) was calculated by dividing the serum concentration by the respective daily dose. Since the C/D-ratio represents the serum concentration per each mg LEV given, it allows inter-patient comparisons across varying doses, intra-patient