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Intrapatient variation in antiepileptic drug plasma concentration after generic substitution *vs* stable brand-name drug regimens

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ABSTRACT

Generic substitution of antiepileptic drugs (AEDs) is still a matter of controversy and concern among clinicians and patients. We aimed to assess intrasubject variation in plasma concentrations of lamotrigine (LTG), levetiracetam (LEV) and topiramate (TPM) after generic substitution compared with a stable brand-name drug regimen in a population of patients with epilepsy. A retrospective analysis was performed on prospectively collected and stored data from our therapeutic drug monitoring (TDM) database for the years 2009–2014. The main outcome variable was the proportion of patients who, after switching from branded to generic formulations, showed a greater than ±20% change in AED plasma concentrations compared to the proportion of control patients showing a change in AED plasma concentrations of the same extent while receiving stable branded formulations over repeated TDM tests. Fifty patients on LTG, 27 on LEV and 16 on TPM showing at least one TDM test while receiving generic products fulfilled the inclusion/exclusion criteria for the analysis and were compared with 200 control patients for LTG, 120 for LEV and 80 for TPM. The proportion of patients showing an intrasubject change greater than ±20% in AED plasma concentrations was similar in the brand name *vs* generic group compared with the control one for LTG (22% *vs* 33%) and LEV (44% vs 38%), while it was higher in the control group for TPM (41% vs 6%, $p < 0.01$). These are the first data in the literature about the within-patient variation in steady-state plasma concentrations of a series of stable treatments with brand-name AEDs in a real clinical setting. In conclusion, a significant interday variability in intrapatient LTG, LEV and TPM plasma concentrations can be observed even in patients stabilized with the same brand name product over time. This suggests that any change in plasma AED concentration and possible related clinical effects after generic substitution may be not necessarily related to the switch. Our results should be confirmed by large, prospective, blinded, randomized controlled studies in people with epilepsy.

1. Introduction

Generic substitution of antiepileptic drugs (AEDs) in the treatment of epilepsy is still controversial due to the lack of consensus and clear guidance for clinicians (Privitera, 2013; Shaw and Hartman, 2010). Retrospective studies and anecdotal reports suggested a potential relationship between brand-name *vs* generic AED switching and adverse effects, especially loss of seizure control, raising concerns among clinicians and patients about the use of generic formulations. A few prospective randomized studies did not confirm the safety risks shown in observational studies, but they must be considered cautiously due to methodological flaws, including small patient samples, short follow-ups and recall bias from subjective reports (Kesselheim et al., 2010; Steinhoff et al., 2009; Talati et al., 2012; Yamada and Welty, 2011). As a result of these potentially negative outcomes, several scientific societies and medicine agencies discouraged the mandatory substitution of AEDs in specific patients and certain situations (Shaw and Hartman, 2010).

Both old and newer AEDs are considered by most physicians as agents with a not wide therapeutic index (Heaney and Sander, 2007; Jankovic and Ignjatovic Ristic, 2015), which implies that even small variations in their bioavailability could result in clinically significant changes in drug plasma concentrations and matched

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therapeutic and/or toxic effects. Current international standardized requirements for approval of generic drugs are sufficiently strict that only small changes (within 10%) in plasma drug concentrations can be expected between brand-name and generic products (Perucca et al., 2006; Shaw and Hartman, 2010). This variability may be modest when compared with potential intrasubject "real life" variation in AED plasma concentrations over time, even with the same drug formulation (Perucca et al., 2006). However, since generic formulations are not required to be bioequivalent to one another, it has been argued that AED generic to generic switches (a common practice, as pharmacies often change their supplies based on prices) could produce much larger plasma concentration swings than allowed for testing brand name to generic substitutions (Bialer and Midha, 2010), contributing to potential adverse effects (Talati et al., 2012). More recently, the UK Commission on Human Medicines has proposed the subdivision of AEDs into three categories based on therapeutic index, solubility, and absorption to help clinicians decide whether it is necessary to maintain continuity of supply of a specific manufacturer's product. All the new AEDs were included in the moderate-to-low risk category 2 or 3 (Commission on Human Medicines UK, 2013).

Sparse observations from our AED therapeutic drug monitoring (TDM) service suggested us that changes in plasma AED concentrations after generic substitution might be no greater than those experienced by patients with epilepsy for whom no such substitution is prescribed. To test this hypothesis, we retrospectively examined intrapatient variation over time of prospectively monitored lamotrigine (LTG), levetiracetam (LEV) and topiramate (TPM) plasma concentrations in patients switched from brand-name to generic products and we compared it to within-subject variability in plasma drug concentrations of stable brand-name products in our TDM setting.

2. Material and methods

2.1. Data source

We retrospectively analyzed data stored in our TDM database from a population of patients with epilepsy referred to the Laboratory of Clinical Neuropharmacology for routine AED monitoring between January 2009 and October 2014. The study was approved by the Ethics Committee of the Bologna Local Health Trust.

2.2. Blood sampling and analysis

Blood specimens were prospectively drawn from patients in our Institute and external clinical centers; plasma was separated and stored at 4 °C in our laboratory until AED analysis (which was carried out within two weeks). TPM and LEV plasma concentrations were analyzed by home-made high pressure liquid chromatography–mass spectrometry and spectrophotometry (UV) methods, respectively, as previously described (Contin et al., 2001, 2008). LTG plasma concentration was determined by HPLC-UV using a commercially available kit (Chromsystems, 2007). For all AED plasma concentration measurements our laboratory adhered to the LGC Standards proficiency testing external quality control schemes (Bury, Lancashire, UK).

Information about daily AED dose, type of formulations, time of administration of the last dose, time of blood sampling, potential concomitant treatments, adverse effects referred by patients as present at the time of blood samplings were recorded on *ad hoc* electronic request forms, with mandatory fields to be completed, by nurses trained in epilepsy as part of the TDM process.

2.3. Subjects

Patients aged ≥18 years on chronic (>1 month) treatment with LEV, LTG, TPM, either alone or in combination with other AEDs were included in the intrasubject analysis if they had undergone at least one TDM test on generic formulation and one TDM on branded formulation comparable for:

(a) daily dose of LEV, LTG, TPM and possible concomitant AED and non-AED treatments;
(b) body weight (within ±5% variation);
(c) venous blood sampling time between 8 and 9 AM, before the first morning dose of AED treatment;
(d) last evening dose of LTG, LEV, TPM between 8 and 9 PM.

Exclusion criteria were: pregnancy or lactation, presence of concomitant acute diseases, liver or kidney transplantation, dialysis treatment, known or suspected history of poor treatment adherence.

The control group included patients treated with the same branded formulation of the three considered AEDs over consecutive TDM tests, randomly picked from the database, applying the same inclusion and exclusion criteria as above. At least 4 controls per case were included (Machin et al., 2009).

2.4. Main outcome variables and statistical analysis

The main outcome variable was the proportion of patients who after brand-to-generic switching showed a greater than ±20% change in LEV, LTG, TPM plasma concentrations, calculated as:

Δ% (brand name *vs* generic) = [(brand name plasma drug concentration – generic plasma drug concentration)/brand name plasma drug concentration] × 100. This variable was compared to the proportion of control patients showing a greater than ±20% change in above AED plasma concentrations while receiving stable branded formulations over repeated TDM tests, calculated as: Δ% (brand name *vs* brand name)=[(1st test plasma drug concentration – 2nd test plasma drug concentration)/1st test plasma drug concentration] × 100.

Comparison of the main outcome variable between the two patient groups was performed by the chi-square test. Clinical and therapeutic variables were compared between the two groups by the Student *t* test or the Mann–Whitney rank sum test, whenever appropriate. Data are expressed as mean ± standard deviation or median (25–75 percentiles). Significance was set at $p < 0.05$.

3. Results

Results of our search in the TDM database are summarized in Fig. 1. Fifty patients on LTG, 27 on LEV and 16 on TPM showing at least one TDM test while receiving generic products (groups A) fulfilled the inclusion/exclusion criteria for the analysis. In addition, 200 control patients (groups B) treated with stable branded formulations over repeated TDM tests were included for LTG, 120 for LEV and 80 for TPM (Table 1). For LTG and TPM, groups A and B were comparable for all the considered demographic and clinical variables. For LEV, the two groups showed statistically significant differences in age and time interval between intrasubject TDM tests.

The types of treatment, i.e. distribution of monotherapies and concomitant AEDs, were similar between groups A and B for all the three AEDs. Cardiovascular drugs, namely ACE inhibitors and antihypertensives (beta-blocking agents and calcium antagonists) were the most frequently coadministered non-AED agents in the overall patient population, followed by gastroprotectors (proton pump