Title:

Changed Constitution without change in Brand Name - the Risk of Generics in
Epilepsy

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Abstract:

Purpose: Lamotrigine (LTG) is an Anti Epileptic Medication (AEM) for which blood levels are helpful for optimal dosing. In late 2010, patients attending an epilepsy clinic were becoming toxic without obvious cause. This paper reports altered levels without change in regimen and provides unexpected findings.

Methods: Patients with elevated LTG blood levels were assessed to determine change in AEM regimen or generic substitution. Method of blood level determination was reviewed and the company (GlaxoSmithKline) contacted regarding change in source of medication.

Principal Results: The sample comprised 18 patients; mean age 40 ± 16 years, mean daily LTG dose 493 ± 218 mg. Mean serum LTG concentrations from August 2010 to February 2011 [$91.8 \pm 17.7 \mu\text{mol.L}^{-1}$, range 69.9-133.7 $\mu\text{mol.L}^{-1}$] were significantly higher than those from January 2010 to July 2010 [$50.3 \pm 9.1 \mu\text{mol.L}^{-1}$, range 32-60.1 $\mu\text{mol.L}^{-1}$], $p < 0.0001$. All patients received parent product (Lamictal®) and the method of LTG blood level determination was unchanged. GlaxoSmithKline confirmed that Lamictal® was sourced from a different site.

Conclusions: These results indicate that, even using a parent compound, AEM levels can fluctuate if the product source has changed, resulting in toxicity. It also highlights the value of determining AEM levels and the risks attached to generic substitution.

Introduction:

Generic compounds are considered bioequivalent versions of brand name drugs that offer patients identical but alternative compounds at a lower cost (Crawford et al., 2006; Sanker et al., 2010). Generic compounds constitute approximately two-thirds of all prescriptions dispensed in the USA but account for < 20% of total pharmaceutical expenditure (Generic Pharmaceutical Association, 2011; Godman et al., 2010). Similarly, in many European countries, generic compounds account for ~ 40% of pharmaceutical dispensing but < 20% of costs (Godman et al., 2010).

A number of studies have raised concerns over generic substitution of antiepileptic medications (AEMs). Switching from brand name to generic AEMs has been associated with increased toxicity (Andermann et al., 2007), breakthrough seizures (Andermann et al., 2007; Berg et al., 2008), increased health care costs due to increased physician visits and/or hospitalisations (Helmerts et al., 2010; LeLorier et al., 2008) and switching back to brand names due to poor acceptance of generics (Berg et al., 2008; LeLorier et al., 2008). Factors that may alter the bioequivalence of generic when compared to brand name AEMs include low water solubility, a narrow therapeutic window due to nonlinear pharmacokinetics and drug interaction with other AEMs (LeLorier et al., 2008; Sankar et al., 2010). Non-bioequivalence of generic AEMs presumably occurs from differences in the manufacturing process resulting in variability of the bioavailability of a generic preparation (Sankar et al., 2010).

The present study reports a series of 18 patients on stable lamotrigine (LTG) (branded product, Lamictal®) (GlaxoSmithKline, 2010) monotherapy or Lamictal® and other AEM combinations, who were found to have significant increases in serum LTG concentrations, following therapeutic drug monitoring with and without the presence of clinical toxicity in the 6-month period following August 1st 2010.

Methods:

Eighteen consecutive patients with generalized or partial seizures attending a private neurology and epilepsy clinic in Sydney, Australia, underwent routine therapeutic drug monitoring of Lamictal® brand monotherapy or Lamictal® combination therapy during 2010. All patients underwent at least one 'trough' serum LTG level (blood collected > 6 hours after last oral Lamictal® dose) prior to August 1st 2010 and after August 1st 2010. Serum LTG concentration measurements were conducted at the same laboratory for all patients. Upon recognition of altered LTG blood levels, without adequate explanation, on stable dosage of medications concerns were raised regarding (i) brand substitution, (ii) laboratory error with altered measurement technique, or (iii) altered constitution of the LTG formulation.

Each patient was questioned regarding brand substitution to confirm maintenance of parent compound or generic substitution. The laboratory was interrogated regarding changes in methodology, source of reagents or equipment used to determine LTG blood levels. The pharmaceutical manufacturer of Lamictal® was approached to seek clarification whether the formulation or source of product had been altered.

A retrospective review of serum LTG concentrations for all 18 patients was conducted to compare levels prior to and after August 1st 2010. The highest serum LTG concentration recorded for each patient between January 1st 2010 and August 1st 2010 was compared to the highest serum concentration recorded for each patient for the six months following August 1st 2010 (through to February 1st 2011). Statistical analysis was performed using a paired 't-test' to compare differences in means of serum LTG concentrations for the two time periods.

Results:

The demographics including AED therapy of all 18 patients is shown in Table 1. Concomitant medications included valproate (8 patients), levetiracetam (8 patients), gabapentin (4 patients) and 1 patient for each of topiramate, oxcarbazepine (OXC), carbamazepine, lacosamide and primidone. The mean daily dose of LTG for the cohort was 493 mg (SD 218, range 150-800 mg).

The median number of serum LTG analyses per patient was 2 (range 1-5) for the time period January 1st to August 1st 2010 and 3 (range 1-6) for the time period August 1st 2010 to February 1st 2011. Figure 1 compares the highest serum LTG concentration recorded for each patient for the two time periods. The mean of the highest serum LTG concentration for the time period August 1st 2010 to February 1st 2011 [mean 91.8 $\mu\text{mol.L}^{-1}$ (SD 17.7, range 69.9 to 133.7 $\mu\text{mol.L}^{-1}$)] was significantly higher than the mean of the highest serum LTG concentration for the time period January 1st 2010 to August 1st 2010 [mean 50.3 $\mu\text{mol.L}^{-1}$ (SD 9.1, range 32 to 60.1 $\mu\text{mol.L}^{-1}$), $p < 0.0001$]. The dose of LTG was reduced in 9 patients after recognition of symptoms of toxicity in 6, such as fatigue, ataxia and impaired cognition, and unacceptably high LTG levels in 3 asymptomatic patients.

It was confirmed that all patients remained on parent compound, Lamictal[®], in concert with prescriptions which indicated that brand substitution was not allowed. LTG and AEM doses were stable for all patients during the period January 1st to August 1st 2010 with the exception of one patient who had OXC withdrawn during the early period of 2010. The laboratory which measured all LTG samples, within this population had not altered methodology, reagents used or equipment employed. The

pharmaceutical company confirmed that the source of Lamictal® had altered during the time period in question.

Discussion:

Previous studies have shown that substitution between parent, brand name AEMs to generic formulations may be associated with clinical adverse events, including drug toxicity (Andermann et al., 2007; LeLorier et al., 2008). Prescription of LTG (both parent compound and generic formulation) in Australia requires government authority prescription for subsidized availability under the Pharmaceutical Benefits Scheme (publically funded formulary) with the physician retaining the right to tick a box, on the prescription, disallowing brand substitution. For this reason, all the patients in this report had the box, on their prescription, marked to confirm that 'brand substitution was not permitted'. This was confirmed with each patient, at the time of review, establishing that all patients reported in this survey were on parent compound Lamictal[®]. To the best of our knowledge, this is the first study to report significant changes in blood levels of LTG, and evolution of toxicity, associated with continued use of stable dosing of the parent compound Lamictal[®].

Alternative explanations, such as a significant treatment modification, for example an increase in valproate dose, known to increase the half-life of LTG (Beran 1999), were excluded. The same laboratory which measured all LTG levels within this study was blinded to dosages or use of concomitant medications (also measured in a single but different laboratory to the one measuring LTG). The laboratory measuring LTG levels confirmed that it had not altered its methodology, equipment or reagents used and had maintained standard procedure for all 18 patients. GlaxoSmithKline (GSK) acknowledged that the site of manufacture of Lamictal[®] had changed during the time period under review. GSK also confirmed that production of Lamictal[®] conformed to

the required Therapeutics Goods Administration standards for Australia. With all other potential variables being excluded, it seems reasonable to assume that the oral bioavailability of Lamictal® was modified by the changed site of manufacture. While the active ingredient, LTG, may have remained static, within the formulation, it is feasible to presume that the increased blood levels of LTG resulted from enhanced bioavailability consequent to changed incipient within the product.

Generic compounds are deemed bioequivalent with brand name compounds if the 90% confidence intervals (CI) of generic/brand name reference ratios for the area under plasma concentration-time curve (AUC) and Cmax fall within an 80% to 125% range (Sankar et al., 2010). This is based on an assumption that if the rate and extent of absorption of generic compounds fall within this (-20 to +25%) range there will be no significant differences in therapeutic effect or tolerability (Sankar et al., 2010). The advantages to government regulatory bodies, in supporting generic compounds, include potential cost savings and the convenience of using generic names, as opposed to brand names (Crawford et al., 2006; Sankar et al., 2010), on prescriptions. Disadvantages may include variability of individual patient responses (Sankar et al., 2010), breakthrough seizures (Andermann et al., 2007; Berg et al., 2008) and drug toxicity (Andermann et al., 2007).

LTG has proven efficacy in the treatment of generalized and partial seizures (French et al., 2004) and is currently available as multiple approved generic compounds (Sankar et al., 2010). The breakdown of seizure types, namely 10:8, generalized : partial seizures, respectively, for this cohort, reflects the increased use of LTG for generalized epilepsy. LTG has high oral bioavailability (GlaxoSmithKline 2010;

Rambeck & Wolf 1993) after oral administration but low water solubility (GlaxoSmithKline, 2010; Sankar et al., 2010), the latter of which is a potential risk factor for adverse effects from generic substitution (Sankar et al., 2010). LTG undergoes linear pharmacokinetics at therapeutic doses (French et al., 2004; GlaxoSmithKline, 2010; Rambeck & Wolf 1993) and is predominantly metabolized by hepatic glucuronide conjugation (French et al., 2004; GlaxoSmithKline, 2010; Rambeck & Wolf 1993). Its metabolic clearance is increased by enzyme inducing AEMs such as phenytoin and carbamazepine and decreased by the addition of valproate (GlaxoSmithKline 2010; Rambeck & Wolf 1993). One of the patients in this study had OXC, also an enzyme inducing AEM, withdrawn early in 2010 but had stable dosing in the 2 months before the study period in question. The reference range for therapeutic plasma concentrations of LTG is often cited as 3-14 mg.L⁻¹ (~12-55 µmol.L⁻¹) (Morris et al., 1998) with the clinic in this study using a tighter reference range of 40-60 µmol.L⁻¹ (Beran 1999). Dose-related side-effects have been reported to appear at concentrations > 15 mg.L⁻¹ (60 µmol.L⁻¹) (Krasowski 2010; Morris et al., 1998) although in clinical practice patients may tolerate higher concentrations with clinical benefit and without signs of toxicity (Søndergaard Khinchi et al., 2008). The clinical utility of therapeutic drug monitoring for many AEMs is controversial but may be justified for AEMs such as LTG in which a concentration threshold for side-effects may exist (Krasowski 2010). In the present case series, therapeutic drug monitoring was crucial in the recognition of therapeutic and/or clinical drug toxicity, which required LTG dosage reduction in some patients.

In conclusion, we report a case series of 18 patients on stable Lamictal® therapy who developed significant increases in serum LTG concentrations presumably due to a

change in site of Lamictal® manufacture and presumed altered compound incipient. Therapeutic drug monitoring of LTG is likely to be of value in patients experiencing symptoms of toxicity and in those switching from Lamictal® to a generic formulation. The present study raises concern that switching from Lamictal® to a generic compound may be associated with adverse clinical effects and should probably be discouraged.

Disclosure of Conflicts of Interest:

None of the authors has any conflict of interest to disclose.

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Table 1. Demographics of study population

	Numbers (n=18)	Male	Female	Mean	SD	Range	Median
Age (years)				40	16	11 -- 74	
Gender		6	12				
Generalised Seizures	10						
Partial Seizures	8						
Lamictal [®] dose (mg)				493	218	150 - 800	
No. of Pts. On Monotherapy	4						
No. of Pts. On 2 Antiepileptic Medication	6						
No. of Pts. On 3 Antiepileptic Medication	5						
No. of Pts. On 4 Antiepileptic Medication	3						
No. of blood tests before 01/08/2010						1 - 5	2
No. of blood tests after 01/08/2010						1 - 6	3

Figure 1