Epilepsy Research (2012) **98**, 269—272

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

SHORT COMMUNICATION

Changed constitution without change in brand name — The risk of generics in epilepsy

Vishal Patel[a], **Dennis J. Cordato**[a], **Manu Dias**[a], **Roy G. Beran**[a,b,c,*]

[a] *Department of Neurophysiology, Liverpool Hospital, Liverpool, NSW, Australia*
[b] *School of Medicine, Griffith University, Queensland, Australia*
[c] *Strategic Health Evaluators, Chatswood, NSW, Australia*

Received 8 September 2011; received in revised form 20 September 2011; accepted 26 September 2011
Available online 24 October 2011

KEYWORDS
Lamotrigine;
Blood levels;
Generics;
Toxicity;
Incipient formulation

Summary
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 [$91.8 \pm 17.7\ \mu mol\ L^{-1}$, range 69.9—$133.7\ \mu mol\ L^{-1}$] were significantly higher than those from January 2010 to July 2010 [$50.3 \pm 9.1\ \mu mol\ L^{-1}$, range 32—$60.1\ \mu mol\ L^{-1}$), $p < 0.0001$]. 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 offering patients identical but alternative compounds at lower cost (Crawford et al., 2006; Sankar and Glauser, 2010). They 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).

Some studies have raised concerns over generic substitution of anti epileptic medications (AEMs). Switching from brand name to generic AEMs has been associated with

* Corresponding author at: PO Box-598, North Bridge, New South Wales 1560, Australia. Tel.: +61 2 97283650; fax: +61 2 94131353.
E-mail address: roy.beran@unsw.edu.au (R.G. Beran).

0920-1211/$ — see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.eplepsyres.2011.09.019

toxicity (Andermann et al., 2007), breakthrough seizures (Andermann et al., 2007; Berg et al., 2008), increased health costs due to increased physician visits and/or hospitalisations (Helmers et al., 2010; LeLorier et al., 2008) and reverting to brand names due to poor acceptance of generics (Berg et al., 2008; LeLorier et al., 2008). Factors altering bioequivalence of generic, when compared to brand name, AEMs include low water solubility, narrow therapeutic window from nonlinear pharmacokinetics and drug interactions (LeLorier et al., 2008; Sankar and Glauser, 2010). Non-bioequivalence of generic AEMs presumably occurs from differences in the manufacturing process causing variability of the bioavailability of a generic preparation (Sankar and Glauser, 2010).

This study reports 18 patients on stable lamotrigine (LTG) (branded product, Lamictal®) (GlaxoSmithKline, 2010) monotherapy or Lamictal® and other AEM combinations, found to have significant increases in serum LTG concentrations, following therapeutic drug monitoring, with and without 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 h post-dose) prior to, and after, August 1st 2010. Serum LTG concentration measurements were conducted at the same laboratory. 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 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 clarify whether the formulation or source of product was altered.

Retrospective review of serum LTG concentrations, for all 18 patients, compared 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 their highest serum concentration recorded for the six months following August 1st 2010 (through to February 1st 2011). Statistical analysis used a paired '*t*-test' to compare mean differences of serum LTG concentrations for the two periods.

Results

Demographics, including AED therapy of all patients, are shown in Table 1. Concomitant medications included: valproate ($n = 8$); levetiracetam ($n = 8$); gabapentin ($n = 4$); and 1 patient for each of topiramate, oxcarbazepine (OXC), carbamazepine, lacosamide and primidone. Mean daily LTG dose 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) from January 1st to August 1st 2010 and 3 (range 1—6) from August 1st 2010 to February 1st 2011. Fig. 1 compares the highest serum LTG concentration for each patient for the two periods. The mean of the highest serum LTG concentration from August 1st 2010 to February 1st 2011 [mean 91.8 μmol L^{-1} (SD 17.7, range 69.9—133.7 μmol L^{-1})] was significantly higher than the mean of the highest serum LTG concentration from January 1st 2010 to August 1st 2010 [mean 50.3 μmol L^{-1} (SD 9.1, range 32—60.1 μmol L^{-1}), $p < 0.0001$]. LTG dose was reduced in 9 patients due to reported toxicity in 6, including 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®. LTG and AEM doses were stable for all patients during the period, January 1st to August 1st 2010, except for 1 patient who had OXC withdrawn during the early period of 2010. The laboratory which measured all LTG samples had not altered methodology, reagents 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

Table 1 Demographics of study population.

	Numbers ($n = 18$)	Male	Female	Mean	SD	Range	Median
Age (years)				40	16	11—74	
Gender		6	12				
Generalized 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