Epilepsy Research (2014) **108**, 1637—1641

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

Conversion from immediate-release to extended-release lamotrigine improves seizure control

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Received 16 January 2014; received in revised form 15 July 2014; accepted 18 August 2014
Available online 27 August 2014

KEYWORDS
Epilepsy;
Immediate-release lamotrigine;
Extended-release lamotrigine;
Seizure frequency;
Drug-resistance;
Toxicity

Abstract
Background: Immediate release lamotrigine (LTG-IR) dosing can be limited by peak toxicity. It is thought that peak levels are responsible for some adverse effects such as dizziness, blurred vision, double vision and unsteadiness. At the same time, trough levels may be associated with reduced seizure threshold. The use of extended release lamotrigine (LTG-XR) to replace LTG-IR will be associated with less fluctuation in drug levels-lower peak levels may reduce adverse effects and higher trough levels may improve seizure control. This hypothesis was tested by analyzing seizure control and adverse effects before and after conversion from LTG-IR to LTG-XR in patients who underwent such conversion in 2009—2011.
Methods: We searched our patient database to identify patients converted from LTG-IR to LTG-XR for persistent seizures or adverse effects from August 2009 until December 31, 2011. We included only patients who took LTG-IR and LTG-XR for at least 6 months each. We excluded patients with nonepileptic seizures, progressive cause of epilepsy, or not keeping a seizure record. We collected the following parameters: age at conversion, LTG-IR dose and dosing schedule, duration on that dose, LTG-XR dose and dosing schedule, LTG serum level before and after conversion, duration of LTG-XR treatment, seizure frequency before and after conversion, and change in adverse experience profile. We also recorded baseline AEDs and any AED change during the course of the analysis.
Results: Fifty five patients (26 female) satisfied the inclusion/exclusion criteria. Their mean age was 45 years (range 23 to 86). Ten were on LTG-IR monotherapy, 24 took LTG-IR plus one other AED, most commonly levetiracetam, and the remaining 21 took LTG-IR plus at least 2 other AEDs. The mean LTG-IR dose was 544 mg/day (range 150—1100 mg/day). The mean LTG-IR serum level was 11.6 (available in 53 patients-range 4.6—21 mcg/ml). Twenty six patients were converted to the same dose and one patient took a mixture of LTG-XR and LTG-IR at the same total daily

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http://dx.doi.org/10.1016/j.eplepsyres.2014.08.004

dose, while 21 had their dose slightly increased and 7 had their dose slightly decreased due to adverse effects. The mean serum level after conversion was 11.8 (available in 49 patients-range 2.6—21.2 mcg/ml). As a result of the conversion, 26 patients (47%) experienced ≥50% reduction in seizure frequency. There was a 46% median reduction in seizure frequency overall. Seven patients reported improvement in adverse effects.

Conclusion: A conversion from LTG-IR to LTG-XR can help improve seizure control in some individuals with drug-resistant epilepsy, in addition to improving tolerability. While it is indicated in individuals experiencing peak adverse effects, it should also be considered in patients who have received incomplete seizure control from LTG-IR.

Introduction

Lamotrigine is almost completely absorbed after oral administration. The mean time to peak lamotrigine concentration following oral administration of immediate release lamotrigine (LTG-IR) is 1 to 1.5 h (Tompson et al., 2008). In patients with drug resistant epilepsy who may need higher doses of lamotrigine, peak toxicity may be a limiting factor, accounting for some adverse effects such as dizziness, blurred vision, double vision and unsteadiness. At the same time, trough levels may be associated with reduced seizure threshold and breakthrough seizures. When LTG-IR is given twice daily, the ratio of peak to trough level can be higher than 2 in induced patients (Tompson et al., 2008). While increasing administration frequency to three times daily may help reduce fluctuations, this is also associated with reduced compliance (Cramer et al., 1989). The use of extended release lamotrigine (LTG-XR) to replace LTG-IR may be associated with lower peak levels, thus reducing adverse effects, and with higher trough levels, thus elevating the seizure threshold, which is expected to improve seizure control. We tested this hypothesis by analyzing seizure control and adverse effects before and after conversion from LTG-IR to LTG-XR in patients who underwent such conversion in 2009—2011.

Methods

Patients

We searched our patient database to identify adult patients converted from LTG-IR to LTG-XR for persistent seizures or adverse effects, starting when LTG-XR was first marketed in August 2009 until December 31, 2011. Patients were included only if they used LTG-IR and LTG-XR for a minimum of 6 months each.

We excluded patients with nonepileptic seizures, those with a progressive cause of epilepsy, patients who were not keeping a seizure record, and patients with follow-up duration shorter than 6 months.

Data collection

The main parameters collected were age at conversion, LTG-IR dose and dosing schedule, duration on that dose, LTG-XR dose and dosing schedule, random LTG serum level before and after conversion, duration of LTG-XR treatment, seizure frequency before and after conversion, and change in adverse experience profile. The baseline monthly seizure frequency was calculated from the seizure count in the last 6 months before converting to LTG-XR. The calculated monthly seizure frequency after converting to LTG-XR was based on the number of seizures in the six months following the conversion.

We also recorded baseline concomitant antiepileptic drugs (AEDs) and any AED change during the course of the study.

Statistical analysis

Descriptive statistics summarized mean, median and standard deviation for the population. Seizure frequency and lamotrigine serum concentrations were compared pre- and post-conversion using the paired *t*-test when the distribution of values was approximately normal, and the Wilcoxon signed-rank test when the distribution was not normal. A significant difference was based on two-tailed $p < 0.05$. The comparison of seizure frequency before and after conversion from LTG-IR to LTG-XR was performed for all patients as well as for the subgroup of patients who had no change in total LTG dose or any other AED change in the 6 months before or after transition.

Approval by the institutional review board

The study was approved by the Vanderbilt Human Research Protection Program prior to any data collection.

Results

Patients and AED regimen

Fifty-five patients (26 female) satisfied the inclusion/exclusion criteria. Among patients keeping a seizure diary, the main reasons for exclusion were: financial limitations (18 patients), no follow-up after conversion (13), progressive disorder (3), epilepsy surgery (1 patient). The mean age of qualifiers was 45 years and the median 44 years (range 23—86 years). Forty-five had focal epilepsy, six had idiopathic generalized epilepsy, and four had symptomatic generalized epilepsy. Ten patients were on LTG-IR monotherapy, 24 took one other AED, most commonly levetiracetam (LEV-18 patients), and the remaining 21