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Can physiologic menstrual cycle change serum lamotrigine concentration?

Marjan Asadollahi [a], Mahtab Ramezani [b,*], Ehsan Karimialavijeh [c], Mehrnaz Tavakolian [b], Maryam Ramezani [b]

[a] Assistant Professor of Neurology, Shahid Beheshti University of Medical Sciences, Loghman Hakim Hospital, Department of Neurology, Iran
[b] Shahid Beheshti University of Medical Sciences, Loghman Hakim Hospital, Department of Neurology, Iran
[c] Assistant Professor of Emergency Medicine, Tehran University of Medical Sciences, Shariaty Hospital, Department of Emergency Medicine, Iran

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ABSTRACT

Purpose: The present study aimed to compare the serum LTG levels during the early-/mid-follicular (low estradiol) and mid-luteal (high estradiol) phases of the physiologic menstrual cycle.
Method: In a cross-sectional study, 20 women with epilepsy were recruited. Participants had been on monotherapy with LTG for at least two months. All the subjects had normal menstrual cycles. Blood samples for each patient were taken whilst fasting during the early-/mid-follicular (Days 3–5) and mid-luteal phases (Days 20–24). All samples were analyzed in batched assays. A comparison of the serum LTG levels was carried out using the Mann–Whitney *U* test Data were analyzed with the SPSS program, version 16 (SPSS Inc., Chicago, IL), *p*-values below 0.05 were considered significant.
Results: The mean serum LTG levels for the early-/mid-follicular and mid-luteal phases were 4.28 ± 2.76 mg/ml (SD) and 3.86 ± 2.06 mg/ml (SD), respectively. There was no statistically significant difference in serum LTG level between the (low estradiol) early-/mid-follicular and (high estradiol) mid-luteal phases in our patients (p-value = 0.23).
Conclusion: The serum level of LTG does not alter significantly during the menstrual cycle.

1. Introduction

Lamotrigine (LTG) is a broad-spectrum antiepileptic drug (AED) used to treat various types of epilepsy and psychiatric disorders. In comparison with older AEDs, LTG has been recognized as a drug with only a few side effects during pregnancy. Some of the few reported side effects of LTG are folic acid deficiency and neonatal withdrawal. There is also a small risk of sexual or reproductive dysfunction associated with LTG. Therefore it is a preferable choice for females of childbearing age [1]. LTG is not biotransformed by the hepatic cytochrome P450 system. Instead, it is metabolized almost exclusively by uridine diphosphate glucuronosyltransferase (UGT) enzymes [2]. It has been shown that estrogenic substrates are also metabolized by glucuronidation, and may potentially interact with the metabolism of LTG [3].

Some studies have indicated that oral contraceptives may increase the metabolism of LTG, resulting in a significant decrease in the plasma concentration of LTG [4,5]. This effect is probably related to the ethinyl estradiol content of the combined contraceptive pills. Despite the relatively well-documented effects of the ethinyl estradiol content of combined contraceptive pills on LTG level, there have been few studies regarding the effect of hormonal changes during the physiological menstrual cycle on serum LTG concentration.

The present study aimed to compare the serum LTG levels during the early-/mid-follicular (low estradiol) and mid-luteal (high estradiol) phases of the physiologic menstrual cycle.

2. Method

Over a three-month period between December 2014 and February 2015, as part of a cross-sectional study, 20 women with epilepsy—who were attended the neurology clinic of an urban teaching hospital (Loghman Hakim Hospital)—were recruited. Participants had been on monotherapy with LTG for at least two months. All the subjects had normal menstrual cycles, defined as regular cycles lasting 21–35 days. The exclusion criteria were pregnancy, age of under 18 years, consumption of any hormonal contraceptives or antiepileptic medication except LTG, endocrine diseases, breastfeeding, abnormal liver or renal functioning, and abnormal menstrual cycle.

* Corresponding author. Tel.: +98 9122493628; fax: +98 2155417547.
E-mail address: drmtbramezani@yahoo.com (M. Ramezani).

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The daily dose of LTG was divided into two equal doses to minimize the possible fluctuation of serum LTG level. The individual doses were held unchanged throughout the study.

Blood samples for each patient were taken whilst fasting in the morning (between 8 and 9 AM) before the morning dose, during the early-/mid-follicular (Days 3–5) and mid-luteal phases (Days 20–24). Total serum LTG levels were measured in the same laboratory by high-performance liquid chromatography. To reduce variability, all samples were analyzed in batched assays (ARK Diagnostics, Inc., Fremont, CA). A comparison of the serum LTG levels from the follicular phases and the luteal phase was carried out using the Mann–Whitney U test. Patients were informed regarding the study protocol and written consent was obtained. Data were analyzed with the SPSS program, version 16 (SPSS Inc., Chicago, IL), and p-values below 0.05 were considered significant.

3. Results

Fourteen of the participants had generalized epilepsy and six had focal seizures. Fourteen patients had less than one seizure attack per year, while the other six had more than one seizure attack in a year. Eight cases had been experiencing seizures for less than one year, in another eight cases one-to-five years, and in the final four cases over five years. The characteristics of the patients are summarized in Table 1.

The mean serum LTG levels for the early-/mid-follicular and mid-luteal phases were 4.28 ± 2.76 mg/ml (SD) and 3.86 ± 2.06 mg/ml (SD), respectively. There was no statistically significant difference in serum LTG level between the (low estradiol) early-/mid-follicular and (high estradiol) mid-luteal phases in our patients (p-value = 0.23). The maximal and minimal differences between serum LTG concentrations in the luteal and follicular phases, in a single participant, were 0.45 mg/dl and 1.04 mg/dl, respectively, which was not clinically significant (p-value = 1.96).

4. Discussion

LTG is increasingly used worldwide for both epileptic and psychiatric disorders. Unlike most other antiepileptic drugs, the major route (76%) of elimination of LTG is through conjugation with glucuronidation. This conjugation reaction is catalyzed by uridine diphosphate glucuronosyltransferase [3].

In previous studies, it has been shown that combined oral contraceptives can reduce LTG serum concentration up to 64% [6]. This could be explained by the fact that the estrogenic contents of oral contraceptives are metabolized by glucuronidation [3]. In another study, a 116% increase in LTG plasma concentration was observed, seven days after beginning a treatment period with combined oral contraceptives [5]. However, progesterone-only contraceptive compounds do not reduce LTG serum concentration [6]. Moreover, it has been reported that the serum level-to-dose ratio of LTG may decrease by 40% during pregnancy, probably because of an increased plasma clearance of LTG induced by hormonal changes during pregnancy [7].

There have been few studies into the effects of hormonal changes on serum LTG concentration during the physiologic menstrual cycle. In one study, performed by Herzog et al. on 12 women with epilepsy using LTG, a notable but not significant 31.3% median decline was observed during the mid-luteal phase, compared to the early-/mid-follicular phase, in patients who did not use any oral contraceptives [8]. However, we found that normal estrogenic hormonal fluctuation during the physiologic menstrual cycle does not alter the serum LTG concentration. Indeed, our results are consistent with a number of other reports. In a study that was performed on just two cases, by Reimers et al., the physiologic fluctuations of female sex hormones throughout a normal menstrual cycle were not found to be associated with relevant changes in LTG serum concentration [2]. In another study, three groups of women with epilepsy using LTG monotherapy were evaluated: the first group (n = 7) did not use oral contraceptives; the second group used oral contraceptives (n = 7); and the third group (n = 7) was postmenopausal. Two menstrual cycles were assessed, monitoring LTG levels every other day. There was a higher mean LTG clearance in postmenopausal women, compared with young women not using oral contraceptives. However, their study also showed that there was no significant fluctuation of LTG clearance during the menstrual cycle [1].

The hypothesis has been proposed that, unlike synthetic ethinyl estradiols, natural ones may minimally affect the level of LTG metabolism [8]. Another suggested hypothesis is that the effect of estradiol on LTG may require a much higher estradiol serum concentration than those achieved during a normal menstrual cycle, or during hormone replacement therapy [9]. However, given the conflicting data from other studies, it is difficult to fully support this hypothesis, meaning more research is needed in this context [2].

During pregnancy, the estradiol serum concentration increases by up to 30 times that of the normal level in the menstrual cycle. This effect can result in a significant decrease in LTG concentration during pregnancy [2]. However, several other physiologic changes during pregnancy may affect the metabolism of LTG. In comparison with other AEDs, the changes to LTG clearance are significant [11]. Harden et al. have reported a 94% increase in total LTG clearance, and an 89% rise in free LTG clearance, during pregnancy [12]. In addition, pregnancy causes changes in drug pharmacokinetics, drug absorption, and metabolism. Therefore it would be prudent to actively monitor AED levels, in particular that of LTG, in pregnant woman with epilepsy [12].

Table 1
Clinical characteristics of the patients.

Number of subjects	20
Age (years)	28 ± 4[a]
Duration of menstrual cycle (days)	30 ± 5
Type of epilepsy	Focal (n = 6) Generalized (n = 14)
Lamotrigine dose (mg/day)	300 (225–375)
Follicular phase serum LTG[b] (mg/ml)	4.28 ± 2.76
Luteal phase serum LTG (mg/ml)	3.86 ± 2.06
Last LTG dose to sampling time (hour)	11 ± 1

[a] Mean ± SD.
[b] LTG, lamotrigine.

5. Conclusion

It seems that the serum level of LTG does not alter significantly during the menstrual cycle. Furthermore, it lacks the risk of sexual dysfunction observed in association with other AEDs [10]. Such advantages should be considered in drug selection for women with epilepsy.

Conflict of interest

None declared.

References

[1] Wegner I, Edelbroek PM, Bulk S. Lamotrigine kinetics within the menstrual cycle, after menopause, and with oral contraceptives. Neurology 2009;73(17):1388–93.

[2] Reimers A, Brodtkorb E, Helde G. Lamotrigine serum concentrations throughout the menstrual cycle: a study of 2 cases. J Clin Neuropharmacol 2006;29(3):160–2.
[3] Christensen J, Petrenaite V, Atterman J. Oral contraceptives induce lamotrigine metabolism: evidence from a double-blind, Placebo-controlled trial. Epilepsia 2007;48(3):484–9.
[4] Sabers A, Ohman I, Christensen J. Oral contraceptives reduce lamotrigine plasma levels. Neurology 2003;61:570–1.
[5] Sidhu J, Job S, Singh S. The pharmacokinetic and pharmacodynamic consequences of the co-administration of lamotrigine and a combined oral contraceptive in healthy female subjects. Br J Clin Pharmacol 2006;61:191–9.
[6] Reimers A, Helde G, Brodtkorb E. Ethinyl Estradiol, not progestrones, reduces lamotrigine serum concentrations. Epilepsia 2005;46(9):1414–7.
[7] De Haan GJ, Edelbroek P, Segers J. Gestation-induced changes in lamotrigine pharmacokinetics: a monotherapy study. Neurology 2004;63:571–3.
[8] Herzog AG, Blum AS, Farina EL. Valproate and lamotrigine level variation with menstrual cycle phase and oral contraceptive use. Neurology 2009;72(10):911–4.
[9] Reimers A, Skogvoll E, Sund JK. Drug interactions between lamotrigine and psychoactive drugs: evidence from a therapeutic drug monitoring service. J Clin Psychopharmacol 2005;25:342–8.
[10] Gil-Nagel A, Lopez-Munoz F, Serratosa JM. Effect of lamotrigine on sexual function in patients with epilepsy. Seizure 2006;15:142–9.
[11] Meador KJ, Pennell PB, Harden CL. Pregnancy registries in epilepsy: a consensus statement on health outcomess. Neurology 2008;71:1109–17.
[12] Harden CL, Pennell PB, Koppel BS. Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding. Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology 2009;73:142–9.