

# HORMONES, SEIZURES, AND LAMOTRIGINE: OH, MY!

## Oral Contraceptives Induce Lamotrigine Metabolism: Evidence from a Double-Blind, Placebo-Controlled Trial.

Christensen J, Petrenaite V, Atterman J, Sidenius P, Öhman I, Tomson T, Sabers A. *Epilepsia* 2007;48(3):484–489. **PURPOSE:** This study evaluates the effect of oral contraceptives on lamotrigine (LTG) plasma concentrations and urine excretion of LTG metabolites in a double-blind, placebo-controlled, crossover study in patients with epilepsy. **METHODS:** Women with epilepsy, treated with LTG in monotherapy and taking combination-type oral contraceptives, were randomized to treatment with placebo or a standard combination-type contraceptive pill. The dose-corrected trough plasma concentration of LTG and the ratio of *N*-2-glucuronide/unchanged LTG on urine after 21 days of concomitant placebo treatment was analyzed versus those after 21 days of concomitant treatment with the oral contraceptive pill. **RESULTS:** The mean dose-corrected LTG concentration after placebo treatment was 84% [95% confidence interval (CI), 45–134%] higher than after oral contraceptives, signifying an almost doubling of the concentration after cessation of oral contraceptives. Most of this increase took place within the first week after oral contraceptives were stopped. The *N*-2-glucuronide/LTG ratio in the urine was decreased by 31% (95% CI, –20–61%) when shifting from oral contraceptives to placebo. **CONCLUSIONS:** Cessation of oral contraceptives leads to an 84% increase in the concentration of LTG. In parallel, the excretion of the *N*-2-glucuronide was decreased, indicating that the changes are caused by altered LTG glucuronidation. The change in LTG concentrations was observed within 1 week of the shift of treatment, suggesting that induction and deinduction of LTG glucuronidation is faster than that seen for other metabolic pathways (e.g., cytochrome P450).

## COMMENTARY

Awareness of potential interactions between antiepileptic drugs (AEDs) and combined oral contraceptives (OCs) is long-standing. In the past, the primary concern was in regard to enzyme-inducing AEDs that cause increased elimination of OCs, leading to contraceptive failure. The possibility of a bidirectional interaction, with an OC inducing therapeutic failure of an AED, is a relatively new concept, occurring with the advent of agents that are eliminated by glucuronidation.

Glucuronidation accounts for elimination of 80 to 90 percent of a lamotrigine dose; UGT1A4 catalyzes the formation of the water-soluble *N*-2-glucuronide. Although the effect of OCs on lamotrigine serum concentrations has been reported before in case series (1), this is the first study of women with epilepsy performed as a double-blind, placebo-controlled crossover study. One previous crossover trial was performed in normal healthy controls (4).

This study by Christensen et al. highlights a few important points regarding mechanism. Although not statistically significant, the finding of a 31% decrease in the *N*-2-glucuronide/lamotrigine ratio ( $p = 0.14$ ), when shifting from OCs to placebo, supports the interpretation that there is increased

glucuronidation with OC use. The study also reports substantial interindividual variability in the quantity and rate of alteration in mean dose-corrected lamotrigine concentration, which may be due to different *UGT1A4* genotypes. Two polymorphisms in *UGT1A4* have been described in a German Caucasian population (allele frequency of 0.08 and 0.09) (5). Polymorphism variants may be more or less prominent in other populations as well. In one study of free lamotrigine clearance during pregnancy, racial differences were noted between Black-American and Caucasian-American patients (6). Furthermore, the Christensen et al. study reported that the increase in dose-corrected lamotrigine concentrations occurs just 7 days after cessation of the OCs, suggesting a very rapid time course for deinduction of *UGT1A4*. It is possible that this hormone-driven alteration in biologic activity is due to activation of this enzyme, rather than to traditional induction. Study of the interval between day 1 and day 7 could help clarify the primary mechanism.

Other studies indicate that the estrogen component of OCs is the most likely cause of reduced lamotrigine concentrations (7). However, a role for progestins is also possible. The activity of the UGT families is regulated by a variety of orphan nuclear receptors, including pregnane X receptor. Activation of UGT by progesterone and progesterone metabolites, via these orphan nuclear receptors, may contribute to the increased clearance of lamotrigine during pregnancy (9). However, because OCs use synthetic progestins with different metabolic byproducts, effects via the pregnane X receptor may not occur.

The effects of pregnancy and its accompanying hormone alterations on the lamotrigine clearance have been demonstrated in previous class I or class II studies (6,10,11), with an increase in lamotrigine clearance 94 to 230 percent above baseline. This study describes an 84% higher clearance rate for lamotrigine when coadministered with OCs, which is consistent with other studies (1,4). Similar findings occurred with coadministration of hormone replacement therapy (HRT) in postmenopausal women (12).

Seizure worsening in pregnancies involving lamotrigine use has been reported (13,14), and the International Registry of Antiepileptic Drugs and Pregnancy, or EURAP, observational study reported that AED doses or numbers were more often increased in women on lamotrigine or oxcarbazepine (15). Not coincidentally, oxcarbazepine also undergoes glucuronidation (50%). Studies of the effects of OCs on oxcarbazepine concentrations are lacking. A recent study demonstrated that therapeutic drug monitoring (TDM) of lamotrigine could reduce the risk for increased seizure frequency and that increased seizure frequency was associated with a ratio of <0.65 of pregnant lamotrigine concentration to the baseline preconception-target lamotrigine concentration (6).

OCs employ various estrogens and synthetic progestins; these exogenous hormones are not of the same type or level

as the endogenous hormones achieved during pregnancy. The magnitude of effect of OCs on lamotrigine concentrations does not appear to be quite as large as that of endogenous hormones. Is it still clinically meaningful? Does seizure frequency increase with initiation of OCs? Does clinical toxicity occur when OCs are discontinued permanently or even during the placebo week? Pregnancy studies have reported postpartum toxicity occurring within the first week of delivery (6,13). Sabers et al. reported a clinically relevant change in most of the patients, with either increased seizure frequency or recurrence of seizures following the addition of OCs and adverse effects following OC withdrawal (1). However, this case series of seven women was not random and selection bias may have been an important factor. Although the Christensen et al. study tried to capture clinical consequences, the investigators had too few patients to demonstrate statistical significance. Despite this fact, three patients had seizures during OC weeks but not during placebo weeks.

A prospective clinical trial that investigates whether lowering the plasma AED level with hormonal therapy actually correlates with increased seizure risk is needed. The study ideally would consist of two randomized arms: one group that undergoes TDM with adjustment of AED dosing back to pre-hormone treatment baseline-plasma levels, and another group that does not have TDM or dosage adjustment with introduction of the hormone therapy. Whether this type of study would be ethical needs to be considered, but given that TDM is not routinely used with introduction of hormonal therapy, the study may be feasible. Other unanswered questions that must be addressed include the interaction potential of the several different hormone components of OCs, as well as of patches, implants, progestin-only OCs or injections, and natural progesterone.

As the authors discussed, it is difficult to interpret effects on seizure frequency. Not only bidirectional but tridirectional interactions occur between sex steroid hormones, lamotrigine concentrations, and epilepsy syndrome or seizure frequency. It is likely that each factor can influence the other two. Sidhu et al. reported a decrease in  $C_{max}$  and area-under-curve for levonorgestrel when the combined OC was coadministered with lamotrigine (4).

In hindsight, the phase III trials with lamotrigine should have taken into account not only concomitant AEDs but also coadministration with OCs or HRT. This early insight may have led to differing dosage recommendations at time of initial FDA approval for women on hormonal therapies. Considering that female patients of reproductive age are encouraged to use OCs when participating in drug trials, not tracking this information falls short of adequately studying medication use across both genders and various life stages.

At this juncture without enough scientific evidence, physicians are left with the art of practicing medicine. Women with epilepsy taking lamotrigine should be monitored for seizures

when OCs or HRT are started and for toxicity when OCs or HRT are discontinued. Dosage adjustment to maintain clinical stability may be necessary in these settings. Whether TDM and dosage adjustment according to laboratory findings is warranted is still unknown.

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