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Step Climb Dosing Guidance From Simulation Studies on Lamotrigine Concentration Changes During Pregnancy

Empiric Dosing Strategies to Predict Lamotrigine Concentrations During Pregnancy

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Introduction: Maintaining seizure control with lamotrigine is complicated by altered pharmacokinetics and existence of subpopulations in whom clearance increases or remains constant during pregnancy. Objective: Our objective was to characterize the potential for particular dosing scenarios to lead to increased seizure risk or toxicity. Methods: Lamotrigine pharmacokinetic parameters obtained from our previous study were applied to a one-compartment model structure with subpopulations (75:25%) exhibiting different clearance changes. A single-patient simulation was conducted with typical pharmacokinetic parameter values from each subpopulation. Population-level simulations (N = 48,000) included six dosing scenarios and considered four preconception doses using the R package mrgsolve (Metrum Research Group). Thresholds for efficacy and toxicity were selected as drug concentration that are 65% lower than preconception concentrations and doubling of preconception concentrations, respectively. Results: Individual simulation results demonstrated that without dose increases, concentrations fell below 0.65 at 6-8 weeks in the high clearance change (HC) subpopulation, depending on preconception clearance. While no simulated dosing regimen allowed all women in both subpopulations to maintain preconception concentrations, some regimens provided a more balanced risk profile than others. Predicted concentrations suggested potential increased seizure risk for 7%-100% of women in the HC group depending on preconception dose and subpopulation. Additionally, in 63% of dosing scenarios for women with low clearance change (LC), there was an increased risk of toxicity (34%-100% of women). Significance: A substantial percentage of simulated individuals had concentrations low enough to potentially increase seizure risk or high enough to create toxicity. Early clearance changes indicate possible subpopulation categorization if therapeutic drug monitoring is conducted in the first trimester. An arbitrary "one-size-fits-all" philosophy may not work well for lamotrigine dosing adjustments during pregnancy and reinforces the need for therapeutic drug monitoring until a patient is determined to be in the LC or HC group.

Commentary

In women with epilepsy (WWE), lamotrigine (LTG) is frequently prescribed for its safer anatomical and behavioral teratogenicity profile compared to other anti-seizure medications (ASMs).[1] Seizure occurrence during pregnancy can significantly impact maternal and fetal morbidity and mortality. Worsened seizure control during LTG-exposed pregnancies had been reported in focal and generalized epilepsies in comparison with other ASMs monotherapies (carbamazepine, phenobarbital and valproic acid), including lower likelihood of seizure-freedom (~58%) and more frequent bilateral tonic–clonic seizures (~21%).[2]

An important factor is the occurrence of changes in LTG clearance and metabolization during pregnancy, which can reduce serum concentration below 65% of their preconception baseline values, increasing risk for seizures. As clearance increases, LTG concentrations decrease linearly during pregnancy.

Worsening in seizure control due to these changes can be somewhat prevented/minimized if serum drug monitoring is obtained and doses are adjusted accordingly. However, this is not always available and there is still no guideline on the frequency of monitoring or on the frequency and magnitude of dose adjustments.

A prospective study on 42 pregnant WWE on LTG monotherapy (64% seizure free pre-pregnancy), who underwent monthly serum monitoring and dose adjustments during pregnancy, found that 19% presented worsening in seizure control and 15% had seizure relapse, including bilateral tonic–clonic seizures. An average of 3 LTG dose adjustments during pregnancy was required (range, 0-6), with 20% to 25% increases each time the serum level fell below the

intended level determined for each woman (preconception concentration, whenever available, or the first level obtained upon enrollment in the study).[3]

Lamotrigine, which is primarily metabolized by UGT1A4 (an UDP-glucuronosyltransferase), undergoes clearance changes as early as 5 weeks postconception, highly correlated with estradiol and gestational week.[4] However, not all pregnant WWE present similar percentage changes in LTG concentration: whereas most will present increased clearance (high clearance change group, 77%) a minority will have modest or no significant change in clearance (low clearance change group, 23%). During early pregnancy (up to gestational week 13), clearance increases by 0.115l per hour for every gestational week, with an intersubject variability of 74%.[4] Pregnant WWE in the high clearance change group have a significantly steeper slope for percentage change in clearance in the first trimester, with no differences in percentage change of estradiol between the groups. Upregulation of UGT1A4 enzyme by estradiol is thought to be a potential mechanism for increases in clearance leading to subtherapeutic serum levels, and therefore, risk of seizure recurrence.

It is best practice to determine preconception serum concentration as guidance for ASM adjustments throughout the pregnancy, and to monitor these dose adjustments with repeated serum concentration measurements throughout pregnancy. However, this is not available at all clinical settings. Moreover, delays in access to laboratory results can further hamper its utility to support timely clinical decisions and to avoid risk of seizures and injury from seizures to the mother and the fetus.

The United Kingdom Maternal Death Enquiry (2006-2008) identified that 9 of 11 cases of sudden unexpected death in epilepsy (SUDEP) during pregnancy or postpartum period corresponded to WWE taking LTG (7/9 in monotherapy). This might be related to particularities of prescription profile (including types of epilepsy treated and doses used) rather than a global observation. Indeed, LTG has grown progressively as most recommended and prescribed ASM for WWE worldwide and yet, no additional alarming trends have been reported for increase in SUDEP cases related to LTG-exposed pregnancies. This is likely due to improved awareness of risk among health professionals caring for WWE and a broader recognition for the need of a pro-active approach to prevent worsening of epilepsy control, since most LTG-exposed pregnancies undergo significant clearance changes (i.e., belong to the high change clearance group). There is no data on whether there is also improved access to therapeutic drug monitoring (preconception and during pregnancy) which would allow closer monitoring and timely changes when warranted.

The current study by Barry et al[5] adds to previous simulation reported by Pa et al,[6] which evaluated a single scenario of LTG dose increase regimen (25, 50, and 25 mg per dose for each subsequent trimester) from a preconception dose of 150 mg twice daily (thus, 175 mg, 225 mg, and 250 mg twice daily) and assuming equal clearance rate changes for all simulated pregnancies, as sufficient dose increments to maintain the target LTG serum concentrations.[6] Barry and colleagues simulate, at individual and population levels, various LTG dose adjustment regimens (no-change, double-dose, 25 mg every 2 weeks, 25 mg every 4 weeks, 50 mg every 4 weeks, 100 mg every 4 weeks) to LTG-exposed pregnancies from the 2 known subpopulations of clearance (high and low change) starting from different preconception daily doses (100 mg, 200 mg, 300 mg, 400 mg). Threshold for efficacy risk was set at 65% lower than preconception LTG serum concentrations and threshold for toxicity was set as twice the preconception concentrations.[5]

All 24 dose adjustment scenarios predicted lower than 65% preconception concentration (and risk of seizures) at 3 to 26 weeks' gestation in the high change group, whereas this was observed only in the no-change regimen in the low change group, late in the pregnancy. With LTG dose unchanged in the high clearance change group, 65% lower than preconception LTG levels are expected as early as 6 to 8 weeks, with risk of seizures of 7% to 100% depending on preconception dose. For this subpopulation, the regimen of 100 mg increase every 4 weeks showed the least risk of loss of efficacy.[5] For the low clearance change group, whereas the no-change regimen was considered the best regimen to avoid toxicity, this same regimen predicted a concentration below 65% by 33 weeks of pregnancy, thus potentially increasing risk of loss of efficacy in the third trimester.[5]

Simulation studies overcome (with limitations) the lack of feasibility to perform clinical trials on pharmacokinetics of ASM dose changes in pregnant women and can provide useful insights to guide our management discussions with pregnant WWE on LTG. If serum concentration monitoring is available at preconception and during early pregnancy, high or low clearance change profiles can be suggested, and safer adjustment regimens can be adopted to maintain therapeutic concentrations and efficacy while avoiding toxicity. Whereas seizure recurrence due to lost efficacy is easier to journal by patients and health care providers, toxicity from LTG dose overshoot during pregnancy has not been specifically detailed in current body of literature and might be more difficult to determine as opposed to other ASMs.

Keeping in mind that most WWE will present high LTG clearance changes during pregnancy, the proposed scenarios of predicted concentrations at different dose adjustment regimens can serve as guidance even when serum levels are not available. Altogether, this study provides clinically relevant information for shared decisions in epilepsy and pregnancy care.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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