

PREGNANCY EFFECTS ON LAMOTRIGINE LEVELS

Lamotrigine Clearance during Pregnancy

Tran TA, Leppik IE, Blesi K, Sathanandan ST, Rimmel R
Neurology 2002;59(2):251–255

OBJECTIVE: To evaluate changes in lamotrigine (LTG) clearance before, during, and after pregnancy.

METHODS: Twelve pregnancies that had complete steady-state data before, during, and after pregnancy were evaluated. Data included weight, LTG dose, and LTG blood levels at preconception, during pregnancy, and postpartum, and concomitant use of other antiepileptic drugs (AEDs) and their dosages. Apparent clearance (L/[kg.day]) of LTG was calculated by dose/level/weight for time points at preconception; during the first trimester, second trimester, and third trimester; and postpartum. Apparent clearance was compared between preconception and each of the three trimesters. Statistical analysis was performed by using one-way analysis of variance, the Student–Newman–Keuls test, and the paired Student's *t* test.

RESULTS: An increase in apparent clearance (>65%) was observed between preconception and the second and third trimesters ($p < 0.05$). Eleven pregnancies required higher doses of LTG to maintain therapeutic levels during pregnancy. There was no significant change in apparent clearance between the trimesters. A decrease in apparent clearance was observed between the last two trimesters and postpartum ($p < 0.05$). In the postpartum period, apparent clearances returned to the preconception baseline, and LTG doses were reduced.

CONCLUSION: Pregnancy increases LTG clearance by >50%. This effect occurs early in pregnancy and reverts quickly after delivery. LTG levels should be monitored before, during, and after pregnancy.

COMMENTARY

Tran et al. contributed significantly to the literature on managing women with epilepsy during pregnancy with their recent article documenting lamotrigine (LTG) clearance throughout pregnancy, and including the preconception and postpartum periods. They found that LTG clearance increased by $\geq 65\%$ for most of their 12 subjects between preconception and the first trimester of pregnancy and remained increased at this magnitude until early in the postpartum period, when it quickly returned to the preconception level. Without a change in LTG dosing, some subjects had an increase in clearance and a decline in serum level of almost 90% during pregnancy. Further, the increase in clearance early in pregnancy and the return to baseline clearance after delivery had a rapid time course, as fast as 2 weeks, causing postpartum toxicity in those subjects who had had their dose increased during pregnancy. This information also raises questions about the safety of LTG during pregnancy: is it possibly less teratogenic than other AEDs because the levels decrease quickly and significantly early in pregnancy, and is it less reliable for preventing seizures because the levels decrease dramatically?

The authors reported that many of their subjects did have seizure exacerbations during pregnancy, mandating an increase in LTG dose, but most (10 of 12) were also taking other AEDs; therefore it is not clear that LTG was the only AED level to decline in these subjects, permitting seizure occurrence.

The authors used a formula to determine apparent clearance (AC) for their analysis, which approximates an AUC (area under the curve) by using a “spot” level. They stated that one can use this equation to determine the dose at which the preconception level can be maintained during pregnancy, based on a current LTG level, provided the preconception level, dose, and weight are available. The overall conclusion is that LTG levels can be expected to decline by 65–90% during pregnancy. This is a greater decline than has been seen with other AEDs, and this information alerts the practitioner to monitor the patient carefully during pregnancy both clinically and through the use of serum levels. It also reinforces the need to document an LTG level in women of childbearing potential in anticipation of pregnancy.

by Cynthia L. Harden, M.D.