

DOES INCREASED LEVETIRACETAM CLEARANCE DURING PREGNANCY REQUIRE PLANNED INTERVENTION?

Pharmacokinetics of Levetiracetam During Pregnancy, Delivery, in the Neonatal Period, and Lactation. Tomson T, Palm R, Källén K, Ben-Menachem E, Söderfeldt B, Danielsson B, Johansson R, Luef G, Ohman I. *Epilepsia* 2007;48:1111–1116. **PURPOSE:** To study pharmacokinetics of levetiracetam (LEV) during pregnancy, delivery, lactation, and in the neonatal period. **METHODS:** Fourteen women with epilepsy receiving LEV treatment during pregnancy and lactation contributed with 15 pregnancies to this prospective study in which LEV concentrations in plasma and breast milk were determined. Trough maternal plasma samples were collected each trimester, and at baseline after delivery. Blood samples were obtained at delivery from mothers, from the umbilical cord, and from newborns during 2 days after delivery. LEV concentration was also determined in breast milk and in plasma collected from 11 of the mothers and their suckling infants after birth. **RESULTS:** The umbilical cord/maternal plasma concentration ratios ranged from 0.56 to 2.0 (mean 1.15, $n = 13$). LEV plasma concentrations in the neonates declined with an estimated half-life of 18 h ($n = 13$). The mean milk/maternal plasma concentration ratio was 1.05 (range, 0.78–1.55, $n = 11$). The infant dose of LEV was estimated to 2.4 mg/kg/day, equivalent to 7.9% of the weight-normalized maternal dose. Plasma concentrations in breastfed were approximately 13% of the mother's plasma levels. Maternal plasma concentrations during third trimester were only 40% of baseline concentrations outside pregnancy ($p < 0.001$, $n = 7$). **CONCLUSIONS:** Our observations suggest considerable transplacental transport of LEV and fairly slow elimination in the neonate. Plasma concentrations of LEV in nursed infants are low despite an extensive transfer of LEV into breast milk. Pregnancy appears to enhance the elimination of LEV resulting in marked decline in plasma concentration, which suggests that therapeutic monitoring may be of value.

COMMENTARY

Pregnancy may be associated with increased seizure frequency in close to 20% of women with epilepsy (1). The cause of the escalation in seizure frequency during pregnancy is likely multifactorial and may be related, in part, to a change in antiepileptic drug (AED) clearance and serum concentration. Lamotrigine, in particular, is considerably affected by pregnancy, with a substantial increase in clearance and a drop in serum levels (2,3). This finding is most pronounced in the second and third trimesters when lamotrigine clearance almost doubles (3). The decreased concentration of lamotrigine is accompanied by rising concentrations of its 2-*N*-glucuronide metabolite, suggesting increased metabolism by glucuronidation (2). Oxcarbazepine, another new AED whose metabolism involves glucuronidation, is similarly affected by pregnancy. A small study showed that the concentration of the active moiety during the second and third trimesters is less than half of the concentration after delivery (4). Valproate, which inhibits glucuronidation, reduces the effect of pregnancy on lamotrigine clearance (5). The amplified glucuronidation during the last two trimesters is most likely related to increasingly higher levels of estrogen, which is known to induce glucuronidation, thus reducing the concentration of drugs metabolized through this pathway (6).

Limited information is available regarding the effect of pregnancy on other new AEDs. Among them, levetiracetam is frequently used as an adjunctive treatment for partial and generalized epilepsy, and it recently received European approval as an initial monotherapy to treat partial-onset seizures. Favorable preliminary reports regarding the safety of levetiracetam during pregnancy are likely to encourage levetiracetam use in that setting (7). The current study by Tomson et al. found that levetiracetam clearance was consistently greater during the third trimester. In women whose dose of levetiracetam remained unchanged, the mean levetiracetam serum concentration in the third trimester was 40% of the mean concentration after delivery. Since levetiracetam is not metabolized through glucuronidation, it is not clear why its clearance is so greatly increased. To clarify the mechanism, a prospective study will need to be conducted to measure concentrations of levetiracetam, as well as its metabolites in plasma and urine, through the stages of pregnancy and after delivery.

An important issue is whether the altered clearance of levetiracetam during pregnancy requires intervention to maintain seizure control. Pregnancy-induced changes in lamotrigine clearance and serum concentration have been shown to be very clinically relevant. Several studies have demonstrated increased seizure frequency associated with declining lamotrigine serum levels (8,9). Lamotrigine dose adjustments are necessary after the first trimester and again following delivery (3). In a large study of seizure control during 1,956 pregnancies, women treated with oxcarbazepine and lamotrigine were the most likely to require dose adjustments. The study did not

have enough patients taking levetiracetam to adequately power a separate analysis.

In the study of Tomson and colleagues, only two of seven women had a greater number of seizures during pregnancy, and both also were taking lamotrigine. In four women who took concomitant lamotrigine, the third trimester reduction in AED levels seemed more pronounced for lamotrigine than levetiracetam. While the clinical relevance of AED serum concentration is established for lamotrigine (10), it is not for levetiracetam. Levetiracetam efficacy is evident very early in titration (11), such that the initial target dose is likely to exceed the minimum effective dose for most treatment-responsive patients. The current study points to the need to study a larger cohort of patients to assess the effect of increased levetiracetam clearance during pregnancy on seizure control, but it does not currently provide enough evidence to support levetiracetam dose adjustment during pregnancy.

The study of Tomson and colleagues did not suggest adverse consequences from the extensive transfer of levetiracetam across the placenta and through breast milk. Even though the levetiracetam half-life in neonates was more than double that of adults, the levetiracetam plasma concentration declined rapidly after birth, with no evidence of accumulation. This finding is in accordance with a previous study (12) and should be reassuring to mothers who wish to provide their infants with the benefits of breast milk.

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