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Brief Communication

Lamotrigine in Pregnancy and Lactation: A Case Report

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Summary: *Purpose:* We investigated the effect of pregnancy on the kinetics of lamotrigine (LTG), passage of LTG over the placenta and the excretion of the drug in breast milk.

Methods: We used high-performance liquid chromatography to determine concentrations of LTG in plasma and in breast milk in a woman who was treated with LTG monotherapy during pregnancy and lactation.

Results: Plasma levels of LTG decreased as pregancy progressed. The ratio of dose to plasma concentration was 5.8 times higher at delivery and 3.6 times higher in late pregnancy as compared with 5 months postpartum, suggesting enhanced clearance of LTG during pregnancy. The concentration ratio of umbilical cord to mother's plasma was 1.2 indicating extensive passage of LTG over the placenta. The LTG plasma concentration in the newborn was still 48 h after birth similar to the plasma levels of the mother at delivery and in the umbilical cord. The ratio of milk to plasma concentration was 0.6 2 weeks after delivery and the plasma concentration in the breast-fed child was 25% of the mother's plasma levels. No adverse effects were observed in the newborn.

Conclusions: The kinetics of LTG may be influenced by pregnancy to such a degree that dose adjustments may be indicated. Due to an extensive passage of LTG into breast milk, and a slow elimination in the newborn, LTG concentrations in the nursed infant may reach levels at which pharmacological effects can be expected. **Key Words:** Epilepsy—Pregnancy—Lamotrigine—Pharmacokinetics—Breast milk.

The treatment of epilepsy in pregnant women demands special consideration. The risks of teratogenic effects of the antiepileptic drugs (AEDs) need to be balanced against the hazards for the woman and fetus associated with uncontrolled seizures (1). Furthermore, a rational drug therapy after delivery and during lactation requires knowledge of excretion of the AED in breast milk and of the pharmacokinetics in the newborn. Treatment during pregnancy is complicated by the fact that the kinetics of several drugs is altered during pregnancy (2–4). Considerable information has been accumulated regarding the kinetics of established AEDs during pregnancy and lactation. However, in recent years, several new AEDs have been marketed. Even though they are generally not licensed for use in pregnancy, an increasing number of women will become pregnant whilst taking the new drugs. Lamotrigine (LTG) is one of the new drugs that has become widely used in many countries. A company-sponsored LTG pregnancy registry has been established. Although >50 pregnancies involving prenatal LTG exposure have been included in the registry (5), no data on LTG kinetics in pregnancy and lactation have been published. Such information is essential for therapeutic decisions regarding AED use during pregnancy and lactation. Therefore, we report the kinetics of LTG in pregnancy and lactation in one patient followed prospectively.

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CASE REPORT

A 25-year-old nonsmoking woman (60 kg body weight) developed juvenile myoclonic epilepsy at age 18 years. Initial treatment with clonazepam was unsuccessful, and valproate was substituted as monotherapy. This treatment, however, had to be discontinued due to tremor, excessive weight gain, and irregular menstruation. At age 23 years, the patient's treatment was therefore changed to LTG as monotherapy. She became seizure-free on a LTG dose of 200 mg/day. After 18 months of this treatment, the patient became pregnant. Blood samples for determination of LTG concentrations were drawn from an antecubital vein at monthly intervals throughout the pregnancy. All blood samples were drawn in the morning immediately before the morning dose.

The patient delivered a healthy child in the 41st gestational week. An additional blood sample from the mother was obtained at delivery at the same time a blood sample was taken from the umbilical cord. Capillary blood samples were also obtained from the heels of the newborn 24 and 48 h after delivery.

LTG concentration in breast milk was determined 2 weeks after delivery when the mother had been breast-feeding the infant for >1 week. Before the morning dose of LTG was administered, a blood sample was drawn from the mother and a capillary sample was simultaneously taken from the child. At the same time, before the mother nursed the infant, a sample of breast milk was also taken. The patient was then allowed to nurse the child. A further blood sample from the mother and the child as well as a breast milk sample were obtained after breast-feeding was completed. The patient was than allowed to take her morning dose of LTG.

Additional trough venous blood samples were drawn from the mother 5 weeks and 5 months after delivery. On the latter occasion, the LTG dose had been decreased to 250 mg/day. The patient had received 5 mg folate daily from the beginning of pregnancy until delivery, but no drugs other than LTG.

LTG concentrations in plasma and breast milk were analyzed with reversed-phase high-performance liquid chromatography, as previously described (6). The within-day repeatability (CV) with this method is 10.0% at 7.8 μM and 8.3% at 27.3 μmol/L. The between-day reproducibility (CV) is 9.2% at 7.8 μM and 7.6% at 27.3 μM. The detection limit of the assay is 0.1 μM.

RESULTS

Plasma concentrations of LTG and ratios of dose to plasma concentration in the pregnant woman are shown in Fig. 1. The LTG dose was increased from 200 to 300 mg daily at week 20 in response to the decreasing LTG levels. Despite this dose increase, the patient had a generalized tonic-clonic seizure at week 38. The dose was decreased to 250 mg/day 3 months after delivery, and the LTG plasma concentration on this dose 5 months postpartum was 16 μM.

As shown in Fig. 1, the ratio of dose to plasma concentration was 3.6 times higher at week 37 and 5.8 times higher at delivery as compared with that at 5 months after delivery. The mother's LTG plasma concentration at delivery was 3.3 μM, and the LTG level in plasma from the umbilical cord was 4.0 μM, yielding a ratio of LTG concentration in the umbilical cord to that in the mother's plasma of 1.2. The LTG concentration in the newborn was 4.8 μM 24 h postpartum and only marginally lower (3.7 μM) 48 h after delivery.

LTG concentrations in breast milk and simultaneous plasma concentrations in the mother and the nursed infant are shown in Table 1. The ratio of milk to plasma concentration of LTG was 0.6, whereas the LTG plasma concentration of the nursed infant was ~25% of the mother's LTG concentration. No adverse effects were observed in the newborn.

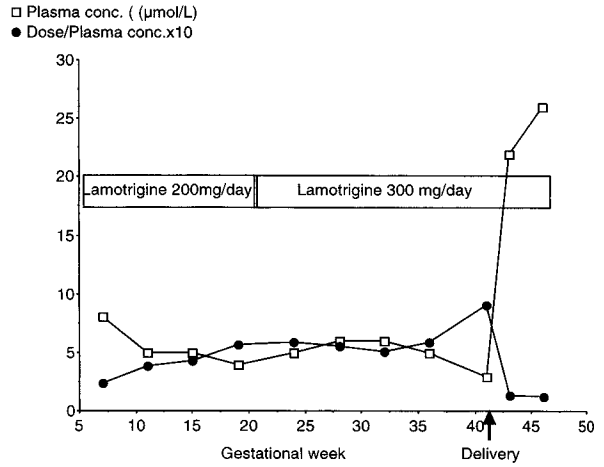

FIG. 1. Dose, plasma concentrations of lamotrigine (LTG) and dose to plasma concentration ratios during and after pregnancy in a 25-year-old woman treated with LTG in monotherapy throughout pregnancy.

DISCUSSION

Our observations in the present case require confirmation in an extended patient series, but some preliminary conclusions may be drawn. If one assumes that data obtained from blood samples drawn 5 months after delivery represent normal conditions, pregnancy appears to affect the kinetics of LTG markedly. Plasma concentrations of LTG decreased steadily as pregnancy proceeded. The changes were so pronounced that they could be expected to have clinical consequences, as indeed was demonstrated by the breakthrough seizure at the end of pregnancy in our patient. Several mechanisms have been suggested for the changes in AED concentrations that have been observed during pregnancy; decreased protein binding and increased clearance are generally considered most important (2–4). No attempt was made to clarify the mechanism in our patient. However, an increase in clearance appears to be the most probable explanation, since LTG is only 50% protein bound (7) and alterations in binding would be expected to have only minor effects. Poor compliance cannot be excluded, but is less likely considering the repeated information given at frequent clinical visists throughout pregnancy and the steady decrease in plasma levels. Finally, folate supplementation during gestation may have interfered with LTG kinetics. However, this is a less probable explanation considering the progressive decrease in LTG concentration depsite a constant folate dosage. Furthermore, we know of no previous report on effects of folate on LTG kinetics.

TABLE 1. *LTG concentrations at time of breast-feeding 2 weeks after delivery*

Sampling time	LTG concentration (μM)		
	Mother's plasma	Nursed infant's plasma	Breast-milk
Before morning dose and during nursing	21.9	5.3	13.6
After completion of nursing	22.1	5.6	12.9

LTG, lamotrigine.

The ratio of almost 1 between the plasma concentrations in umbilical cord and mother at delivery indicates a free passage of LTG over the placenta. Our data furthermore indicate that the newborn's capacity to eliminate LTG is much lower than that which has been reported in adults and in older children. The plasma concentration of LTG in the newborn 48 h after delivery was similar to the plasma level in the umbilical cord at delivery (Table 1). This is not surprising since LTG is metabolized mainly by glucuronidation (8) and the capacity to glucuronidate is not fully developed in newborns (9). In the present case, the plasma concentrations in the newborn may to some degree have been influenced by intake of the drug through breast milk. However, the contribution from breast milk can be assumed to be minor since breastfeeding was not fully established at that time.

Two weeks after delivery, LTG concentration in breast milk was ~60% of the concentration in the mother's plasma. Assuming a daily milk intake of 150 ml/kg/day, the LTG dose to the infant could be estimated to 0.5 mg/kg/day which, according to our data, results in LTG concentrations in the infant at a level at which pharmacological effects may appear.

Our observations demonstrate the importance of monitoring LTG concentrations during pregnancy, even though no clear concentration–effect relationship has been established (10). In addition, newborn infants and breast-fed children should be monitored for possible adverse effects of LTG; if such effects are suspected, blood level monitoring is recommended. Our results furthermore indicate the importance of collecting pharmacokinetic data on the new AEDs to obtain a better basis for rational use of such drugs during pregnancy and after delivery.

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Note: Since the submission of our original manuscript, Rambeck and co-workers (11) have published a study of lamotrigine concentrations in a mother and her newborn child. Their observations are in good agreement with our results.

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