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Pharmacokinetics of Levetiracetam during Pregnancy, Delivery, in the Neonatal Period, and Lactation

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Summary: *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 0.56–2.0 (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. **Key Words:** Epilepsy—Pregnancy—Levetiracetam—Pharmacokinetics—Breast milk.

Levetiracetam (LEV) is a new generation antiepileptic drug initially licensed as adjunctive therapy in patients with refractory partial seizures with or without secondary generalization (French et al., 2004) and now recently in Europe also as monotherapy. Preliminary reports indicate efficacy in other epilepsy syndromes including idiopathic generalized epilepsies (Grunewald, 2005). LEV is not protein bound (Patsalos, 2004), and mainly eliminated by renal excretion, but approximately 30% of the dose is metabolized by enzymatic hydrolysis (Perucca and Johannessen, 2003). The elimination half-life in serum is in the order of 6–8 h.

With its emerging broad-spectrum profile, LEV is becoming increasingly used in women with epilepsy of childbearing potential and thus also during pregnancy (Long, 2003; ten Berg et al., 2005). Nevertheless, information on the pharmacokinetics of LEV during pregnancy and breast-feeding is scarce. A recent study reported pharmacokinetic data from birth and during breast-feeding based on eight women treated with LEV as adjunctive treatment or monotherapy (Johannessen et al., 2005). The umbilical cord:maternal plasma concentration ratio was 1.14 (n = 4) and the milk:maternal plasma concentration ratio 1.00 (n = 7). At 3–5 days after delivery, the breastfed infants had very low LEV plasma concentrations and no adverse effects of breast feeding were noted. These findings are in some contrast to an early case report suggesting a milk:maternal plasma concentration ratio of 3:1 (Krämer et al., 2002). In addition to these partly conflicting data, we still lack information on plasma concentrations of LEV in neonates the first days after birth and, with the exception of preliminary data presented in an abstract (Pennell et al., 2005), the effects of pregnancy on the kinetics of LEV.

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The objective of the present study was to provide further information on the pharmacokinetics of LEV during pregnancy, birth, and lactation, including also data on maternal plasma concentrations throughout pregnancy as well as on the course of LEV plasma levels in neonates during the first days after birth.

SUBJECTS AND METHODS

Altogether 14 women, 21–37 years of age, with epilepsy receiving LEV treatment during pregnancy and lactation contributed with 15 pregnancies to this prospective study. LEV was used as monotherapy in six of the pregnancies and prescribed in combination with other antiepileptic drugs during the remaining nine. Patient characteristics are summarized in Table 1. One pregnancy ended in a stillbirth in gestational week 36. Otherwise, all women had full-term pregnancies, and gave birth to healthy children.

Depending on the time of enrolment, individual willingness to participate, and availability for sampling, the women and their offspring could participate in different parts of this study (Table 1). Hence, in seven pregnancies of six women, maternal plasma concentrations of LEV were obtained during each trimester and at baseline at least 1 month after pregnancy. The median sampling time was gestational week 10 during the first trimester, week 20 during the second, week 32 during the third, and 2 months after delivery at baseline. The LEV dosage remained unchanged throughout the sampling period in all of these pregnancies. Maternal trough plasma samples were available from the third trimester as well as at baseline in five additional pregnancies.

In 13 pregnancies, drug levels were obtained in maternal plasma at delivery and in cord blood.

Plasma levels of LEV were followed after birth in 13 of the newborns and 11 of the mother–child pairs were studied during breast-feeding.

During pregnancy and at baseline, blood samples from the women were drawn before the morning dose. Maternal and umbilical cord blood samples were collected immediately after delivery, and are for obvious reasons thus not trough levels. Capillary blood samples were obtained from the newborns on three occasions during the first 2 days after birth.

Blood and breast milk were collected from mothers 4–23 days after delivery. A blood sample was drawn from the mothers before the morning dose, approximately 10–15 h after the last LEV dose to the mother. A sample of the milk was also taken at the same time. A blood sample was drawn from the infant within 30–120 min after completion of breast-feeding. The mothers were then allowed to take the morning dose of LEV.

LEV concentrations in plasma and breast milk were determined by a liquid chromatographic-mass spectrometric (LC-MS) method (to be published). In brief, 0.1 ml aliquots were mixed with 0.2 ml acetonitrile and centrifuged. The resulting supernatant (6 μl) was injected into the LC-MS system and the protonated molecular ion was monitored. The quantification was done using an internal standard. The detection limit of the assay was 0.3 μmol/L and the measuring range 1–590 μmol/L. The coefficient of variation was 13.2% at 5.9 μmol/L and 2.2% at

TABLE 1. *Characteristics of women treated with levetiracetam (LEV) during pregnancy and drug concentrations at delivery and the first days after*

Patient number	Contributed with data from	Concomitant antiepileptic drugs (mg/day)	LEV dose at baseline / delivery (mg/day)	Maternal LEV plasma at delivery (μmol/L)	Umbilical cord LEV plasma (μmol/L)	Infant LEV plasma concentration				
						6 h after birth	12 h after birth	24 h after birth	36 h after birth	48 h after birth
1	I-IV	Lamotrigine (400)	3,000/3,000	101	184	88	16			12
2	I-IV	None	1,000/1,000	45	50	40	35		14	
3a	I	Lamotrigine (300)	1,000/[a]							
3b	I-IV	Lamotrigine (300)	1,000/1,000	24	35	23	22		19	
4	I-IV	None	2,500/2,500	69	68	50	35		15	
5	I-IV	None	1,000/1,000	39	35	29	18		6	
6	I,III	Lamotrigine (300)	1,000/1,000	21	19	15	12		3	
7	II,III	None	2,500/1,000	11	7					
8	II-IV	Lamotrigine (200)	3,000/2,000	120	142		91	48	26	
9	II-IV	Carbamazepine (1,000)	2,500/3,000	61	66		50		13	
10	III, IV	Tiagabine (30) Clobazam (45) Oxcarbazepine (600)	2,000/2,000	86	87	71	57		27	
11	II-IV	Lamotrigine (400)	2,000/2,000	118	125		97	76	21	
12	II-IV	None	2,500/2,500	26	52	47	33		10	
13	III, IV	None	3,000/3,000	92	148[a]			53		20
14	III	Carbamazepine (1,500)	1,000/1,000	45	25					1

[a]Stillbirth week 36.

I, All trimesters; II, 3rd trimester; III, delivery and neonatal data; IV, breast-feeding.

118 μmol/L. All LEV concentrations were analyzed at the end of the study and this information was thus not available to the treating physician as a basis for decisions on dosage adjustments.

For the seven pregnancies with complete sampling from all trimesters, information on seizure control during and before pregnancy was obtained in retrospect based on medical records.

Statistical analysis

ANOVA (nonparametric, baseline vs. trimesters) was used to analyze changes in serum concentrations during pregnancy. Student's paired *t*-test was used to compare dose/plasma concentration ratios between the third trimester and baseline.

The Institutional Review Board has approved the study and each mother gave her informed consent.

RESULTS

Mean plasma concentrations of LEV during each trimester and at baseline for the seven pregnancies with complete sampling and unchanged dosage are presented in Fig. 1. The mean (±SD) plasma concentration of LEV during the third trimester was 27.5 μmol/L ±15.7, significantly lower than 69.1 ± 37.9 at baseline ($p < 0.01$, $n = 7$). All these women were seizure free during at least 9 months prior to conception, and five remained so throughout pregnancy. Patient no. 1 (Table 1) was seizure free until the 36th gestational week when she had a relapse with complex partial seizures gradually increasing in frequency until a caesarean in week 39. Patient no. 3 had a septicaemia in the late phase of her first pregnancy, which ended in a stillbirth (Table 1, 3a). She had one complex partial seizure during that period but was otherwise seizure free. The decline in maternal plasma concentration of LEV in the third trimester was not more pronounced in these two pregnancies compared with the five

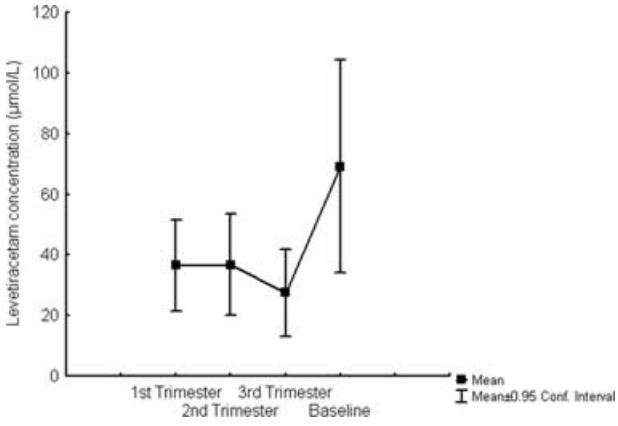

FIG. 1. Plasma concentrations of levetiracetam (LEV) at different stages of pregnancy and at baseline (before or at least 1 month after pregnancy) in 7 pregnancies of 6 women treated with unchanged dosage of LEV throughout the study period.

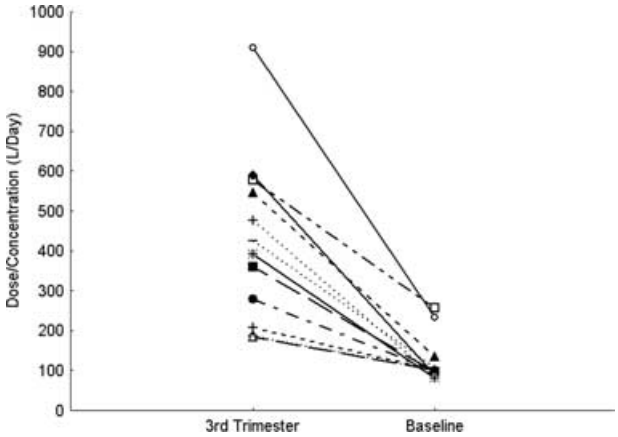

FIG. 2. Apparent clearance of levetiracetam (LEV) (Dose/plasma concentration) during the third trimester and baseline, before or at least 1 month after pregnancy, in 12 women on LEV.

seizure free cases. Lamotrigine was prescribed concomitantly in four of these seven pregnancies including the two with seizures (Table 1). The lamotrigine plasma concentrations declined markedly during pregnancy in all and the dosage was increased in one of the pregnancies (no. 6). In these four pregnancies, the mean lamotrigine dose/plasma concentration ratio at baseline was 17% (range 15–20%) of the dose/plasma concentration ratio in the third trimester.

Among the five additional pregnancies for which maternal plasma concentrations were available only from the third trimester and baseline, the LEV dosage was changed in two after delivery. Therefore, to be able to include also those in the comparison, plasma levels were normalized for dosage by calculation of the apparent clearance (dose/plasma concentration). The apparent clearance of LEV during the third trimester and at baseline is thus presented for the altogether12 pregnancies (the seven with complete data from all trimesters plus the five with third trimester data only) in Fig. 2. Apparent clearance was significantly higher during the third trimester with an increase from mean (±SD) 124.7 ± 57.9 L/Day at baseline to 427.3 ± 211.3 ($p < 0.0001$, $n = 12$).

Maternal and umbilical cord LEV plasma concentrations at delivery and plasma levels in the infants up to 48 h after birth are presented in Table 1. At delivery the umbilical cord to maternal LEV plasma concentration ratio was 1.09 (range 0.64–2.0, $n = 13$). LEV plasma concentrations in the neonates thereafter declined to on average of 20% of the cord plasma levels (range 8–54%) at 36 h postpartum (Fig. 3). The mean elimination half-life of LEV in the neonates was 18 h (range 6–28 h). All but one of the neonates was breast-fed. The decline in LEV plasma concentrations in the nonbreast-fed neonate was however not more rapid than in the other infants (Table 1).

LEV concentrations in breast milk and simultaneous plasma concentrations in the mothers and nursed

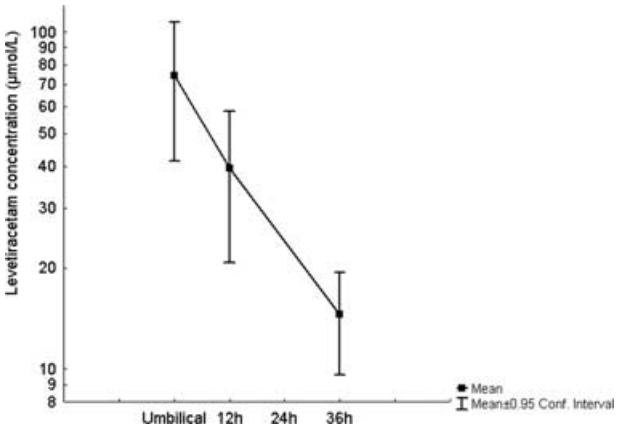

FIG. 3. Log plasma concentrations of levetiracetam (LEV) in cord blood of 12 mothers treated with LEV during pregnancy and in capillary blood of their newborns during the first 36 h after delivery.

infants were available from 11 mother–infant pairs and are presented in Table 2. From 4 up to 23 days after delivery the mean milk:maternal plasma LEV ratio for sampling before nursing was 1.05 (range, 0.78–1.55, n = 11). Assuming a daily milk intake of 150 ml/day/kg the relative infant dose of LEV was estimated to approximately 2.4 mg/kg/day, which is equivalent to 7.9% of the weight-normalized dose received by the mother. LEV plasma concentrations in breastfed infants after nursing ranged from 4 to 20 μmol/L. The infant/maternal plasma concentration ratio after nursing was 0.13 (range 0.07–0.22, n = 10). No adverse effects related to breast-feeding were reported.

DISCUSSION

Our data on LEV concentrations in cord blood confirm observation in a previous slightly smaller study (Johannessen et al., 2005). The mean ratio cord/maternal plasma concentration of LEV was 1.15 in our study, virtually identical to 1.14 in the previous report, indicating a considerable placental transfer of LEV. Likewise, our data from 11 breast-fed infants are in line with the earlier report based on 5 mother–child pairs (Johannessen et al., 2005). We found a mean milk:maternal plasma concentration ratio of LEV of 1.05 compared to 1.00 in the Norwegian study (Johannessen et al., 2005). There are limitations of spot sampling as in these studies compared to measuring excretion of a drug in breast milk over 24 h. LEV plasma concentrations, however, were low in all nursed infants, and on average 13% of maternal plasma concentrations in our study. Hence, ours as well as the results of Johannessen and collaborators are in contrast to data in an early case report suggesting accumulation of LEV in breast milk (Krämer et al., 2002). There was no indication of a similar accumulation in any of the altogether 16 mother–child pairs in our two studies combined. This should be reassuring for mothers considering breast-feeding while on treatment with LEV.

The elimination half-life of plasma LEV was estimated to 18 h in the 13 neonates included in our study. This is longer than the 6–8 h found in adults (Perucca and Johannessen, 2003). This discrepancy is expected as LEV is eliminated mainly unchanged through the kidneys and kidney function not fully developed in neonates (Blackburn 1994). Plasma concentrations in the neonates may also have been influenced by drug intake through breast feeding although there was no indication of a more rapid decline in plasma concentrations of LEV in the only neonate that was not nursed. Furthermore, our estimates of LEV elimination half-lives are similar to the 16–18 h reported in two formula-fed twins, the only available previous data on elimination of LEV in newborns (Allegaert et al., 2006).

We also present data on the course of maternal plasma concentrations of LEV during pregnancy. This is important because pregnancy is known to affect the

TABLE 2. *Levetiracetam (LEV) concentrations and milk:plasma concentration ratios at time of breast-feeding*

		LEV concentration (μmol/L)				Ratios	
Patient number	LEV dose (mg/day)	Time of sampling (days after delivery)	Mother's plasma before nursing	Breast milk before nursing	Nursed infant's plasma after completion of nursing	Milk: plasma LEV concentration	Infant: maternal plasma LEV concentration
1	3,000	23	110	171	13	1.55	0.12
2	1,000	12	61	62	7	1.02	0.12
3b	1,000	15	51	57	9	1.12	0.18
4	2,500	12	104	81	12	0.78	0.12
5	1,000	14	27	34	4	1.26	0.15
8	2,500	13	74	68	13	0.92	0.18
9	2,500	21	73	59	7	0.80	0.10
10	2,000	21	201	210	13	1.04	0.07
11	2,000	4	67	69	[a]	1.02	
12	2,500	10	137	120	12	0.88	0.09
13	3,000	10	91	102	20[b]	1.12	0.22

[a] Data missing.
[b] Sampling before nursing.

pharmacokinetics of other antiepileptic drugs and because such alterations may affect seizure control as well as fetal drug exposure (Tomson, 2005). The only previous data on the impact of pregnancy on the pharmacokinetics of LEV is a preliminary report based on five pregnancies published in abstract form (Pennell et al., 2005). That study suggests an enhanced elimination of LEV during pregnancy. Mean LEV clearance ([mg/kg]/[μg/ml]) at baseline postpartum was 65% of third trimester and 58% of second trimester clearance (Pennell et al., 2005). We found a trend toward a decline in LEV plasma concentrations during the first two trimesters and significantly lower plasma levels in the third compared to baseline. Third trimester plasma concentrations were only 40% of baseline levels in the seven pregnancies with unchanged dosage and complete data for the entire pregnancy. When all 12 pregnancies with data from the third trimester were taken into account, apparent clearance (dose/plasma concentration) was higher during the third trimester compared with baseline in each woman, the mean apparent clearance at baseline being 29% of third trimester values. Unlike Pennell and collaborators (Pennell et al., 2005) we did not include changes in body weight in our calculation of apparent clearance, a fact that could partly explain the more prominent change in apparent clearance in our patients.

Although marked, the decline in LEV concentrations in pregnancy were not as pronounced as the pharmacokinetic alterations reported during pregnancy for lamotrigine (Tomson, 2005) or according to preliminary data for oxcarbazepine (Mazzucchelli, 2006), drugs metabolized by glucuronidation. The observed changes in LEV concentrations, however, are at least as prominent as those seen for drugs metabolized by the cytochrome P450 system, for example, carbamazepine and phenytoin (Tomson, 2005). This increase in apparent clearance of LEV is more than what could be expected based on only an increased renal blood flow in late pregnancy (Anderson, 2005) and indicates that pregnancy may induce the metabolism of LEV. Other mechanisms are also possible for the decline in LEV concentrations, for example, impaired drug absorption. Decreased binding of LEV to serum proteins is, however, not an explanation since LEV is not bound to plasma proteins (Patsalos, 2004). We have not been able to find examples of pharmacokinetics in pregnancy for other drugs eliminated by the same metabolic route as LEV. Whatever the mechanisms may be a decline in plasma concentrations in the order of 60% is likely to be of significance for the efficacy of the drug. Information on seizure control was unfortunately not prospectively collected in the present study and it is difficult to draw conclusions in this respect from only seven pregnancies with complete data from all trimesters. The interpretation is further complicated by the fact that LEV was taken in combination with lamotrigine in four of these pregnancies, including the two with deterioration in seizure control, and the lamotrigine levels seemed to decline more than LEV. The fact that five remained seizure free does not exclude a clinical relevance of the observed decline in LEV serum concentrations. It thus seems advisable to monitor plasma concentrations of LEV during pregnancy to control for changes in its disposition, and the dosage should be reevaluated after delivery if increased during pregnancy.

In conclusion, we have in this larger case-series confirmed previous observations of an extensive transplacental transfer of LEV, of significant transfer into breast milk but low plasma concentrations in nursed infants. We have demonstrated comparatively slow neonatal elimination of LEV and a surprisingly marked decline in maternal plasma concentrations of LEV during pregnancy although the limited number of pregnancies in this study calls for some caution in interpretation. Further studies are needed to confirm in particular the pharmacokinetic alterations during pregnancy. Such studies should preferably include measurement of excretion of LEV and metabolites in the urine to clarify the mechanisms involved.

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