Epilepsia, **41**(6):709–713, 2000
Lippincott Williams & Wilkins, Inc., Baltimore

Clinical Research

Lamotrigine in Pregnancy: Pharmacokinetics During Delivery, in the Neonate, and During Lactation

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Summary: *Purpose:* To investigate the pharmacokinetics of lamotrigine (LTG) during delivery, during the neonatal period, and lactation.

Methods: High-performance liquid chromatography was used to determine plasma and milk levels of LTG in nine pregnant women with epilepsy treated with LTG, and plasma levels in their 10 infants. Samples were obtained at delivery, the first 3 days postpartum, and at breast-feeding 2–3 weeks after delivery.

Results: At delivery, maternal plasma LTG concentrations were similar to those from the umbilical cord, indicating extensive placental transfer of LTG. There was a slow decline in the LTG plasma concentration in the newborn. At 72 h postpartum, median LTG plasma levels in the infants were 75% of the cord plasma levels (range, 50–100%). The median milk/maternal plasma concentration ratio was 0.61 (range, 0.47–0.77) 2–3 weeks after delivery, and the nursed infants maintained LTG plasma concentrations of ~30% (median, range 23–50%) of the mother's plasma levels. Maternal plasma LTG concentrations increased significantly during the first 2 weeks after parturition, the median increase in plasma concentration/dose ratio being 170%.

Conclusions: Our data demonstrate a marked change in maternal LTG kinetics after delivery, possibly reflecting a normalization of an induced metabolism of LTG during pregnancy. LTG is excreted in considerable amounts in breast milk (the dose to the infant can be estimated to ≥0.2–1 mg/kg/day 2–3 weeks postpartum), which in combination with a slow elimination in the infants, may result in LTG plasma concentrations comparable to what is reported during active LTG therapy. No adverse effects were observed in the infants, however. **Key Words:** Epilepsy—Pregnancy—Lamotrigine—Pharmacokinetics—Breast milk.

Lamotrigine (LTG) is a widely used antiepileptic drug (AED) currently available in ~70 countries. With a more widespread use of the drug, an increasing number of women will be exposed to LTG during pregnancy and lactation. An International Lamotrigine Pregnancy Registry has been set up by the manufacturer to collect information about pregnant women exposed to LTG (1). As of March 31, 1999, 167 pregnancies with LTG exposure had been prospectively included. The registry is focusing on pregnancy outcome in terms of birth defects. However, most women who take AEDs during pregnancy continue to do so after delivery. The drugs may thus affect the child, not only in the form of birth defects induced in early fetal life, but also through pharmacologic effects later in pregnancy, after delivery, and during lactation. It is for this reason important to obtain information on transfer of the drug over the placenta, on the capacity of the newborn to eliminate the drug, and on the exposure of the infant to the drug through breast-feeding.

LTG is a phenyltriazine AED structurally unrelated to conventional AEDs. The drug is metabolized primarily by glucoronic acid conjugation in the liver with a negligible first-pass effect. The major metabolite is an inactive 2-*N*-glucuronide conjugate that accounts for ~70% of the total metabolites in urine. Other inactive metabolites are 5-*N*-glucuronide (10%), 2-*N*-methyl metabolite (<1%), and other unidentified minor metabolites (4%). There are no known active metabolites of LTG in humans. LTG is ~55% protein bound, and the volume of distribution is ~1.3 L/kg (2).

Although LTG has been used in hundreds of pregnancies, information on the kinetics at delivery and during the neonatal period and lactation is limited to two case reports (3,4). Both reports suggest a fairly extensive passage of LTG over the placenta and into breast milk. We

Accepted January 26, 2000.
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therefore systematically studied LTG kinetics during delivery, in the neonate, and during lactation in an extended series of patients.

SUBJECTS AND METHODS

Nine patients with epilepsy participated in the study (Table 1). Six had idiopathic generalized epilepsy, one had localization-related epilepsy and two had undetermined types of epilepsy. One patient participated twice, the results of her first pregnancy (no. 6a) have been reported previously (4). All patients were treated with LTG since before conception and were followed prospectively throughout the pregnancy. Doses were adjusted during pregnancy when clinically indicated. All women had uneventful deliveries at full term and gave birth to healthy children.

Blood samples from the mothers and from the umbilical cords were collected at delivery. Capillary blood samples also were obtained from the heel of the newborn at 24, 48, and 72 h after delivery. After 2 weeks, when breast-feeding was established, a blood sample was drawn from the mother and the infant both at the start and after completion of breast-feeding. These plasma samples were drawn 11–15 h after the last LTG dose to the mother (Table 3). Intake of the morning dose of LTG was delayed until after the last blood sample on the day when lactation was studied. Milk samples were obtained on the same occasion. A baseline blood sample, for comparison, was drawn from the mother ≥2 months before (in one mother) or after pregnancy (in eight mothers). LTG concentrations in plasma and breast milk were analysed with reversed-phase high-performance liquid chromatography as previously described (5). The detection limit of the assay is 0.1 μ*M*, and the range of quantification 2–65 μ*M*. The between-day coefficient of variation (CV) is 4.33% at 7.8 μ*M* and 5.7% at 27.3 μ*M*, and the within-run CV is 2.6% at 7.8 μ*M* and 3.3% at 27.3 μ*M*. The within-run CV for small volumes (20 μl) is 16% at 7.7 μ*M* and 10% at 37 μ*M*.

Statistical comparison was conducted using paired *t* test and one-way analysis of variance (ANOVA). The p-values <0.05 were considered significant. The statistical analysis was performed using a Graphpad Prism software version 2.0 (GraphPad Software Inc., San Diego, CA, U.S.A.).

The study was approved by the Ethics Committee at the Karolinska Institute, and all mothers gave their informed consent.

RESULTS

Maternal LTG plasma levels at delivery and levels in the infants 72 h postpartum are shown in Table 2. There was a slow decline in LTG plasma concentrations in the infants after delivery. LTG plasma levels in the infants at 72 h were slightly, although statistically significantly ($p < 0.05$, paired *t* test), lower than in the umbilical cord. The median LTG plasma level at 72 h was 75% (range, 50–100%) compared with that in the umbilical cord.

There was a statistically significant ($p < 0.05$, one-way ANOVA) increase in the maternal plasma concentration/dose ratios from delivery to the sampling period 2–3 weeks after birth (Fig. 1). The median increase was 170% (range, 0–630%). The ratios at delivery also were significantly ($p < 0.05$, one-way ANOVA) lower compared with the baseline values ≥2 months before or after pregnancy. However, patients 2 and 3, both treated with phenytoin (PHT) or carbamazepine (CBZ) in adequate doses in addition to LTG, showed no increase in this ratio after delivery.

The umbilical cord blood/maternal LTG concentration ratio ranged from 0.6 to 1.3 (median, 0.9). LTG concentrations in breast milk and plasma simultaneously obtained from the mother and nursed infant are shown in Table 3. The median milk/maternal plasma LTG ratio was 0.61 (range, 0.50–0.77) before nursing with minor changes thereafter. The minimal amount of LTG ingested by the breast-fed infant was thus estimated to be

TABLE 1. *Characteristics of women with epilepsy treated with lamotrigine during pregnancy and of their newborns*

Patient number	Age (yr) at delivery	Concomitant antiepileptic drugs (mg/day)	Other medications	Gestational age at birth (wk)	Birth weight (g)	Days after birth when breast-feeding was commenced	Smoking during pregnancy
1	28	Carbamazepine (100)	Folic acid, hydroxocobalamin	40	3,700	ND	No
2	43	Phenytoin (325)	Folic acid	42	3,835	ND	No
3	31	Carbamazepine (1400)	Folic acid	42	3,390	First	No
4	20	Valproic acid (1200)		43	2,420	ND	Yes
5	23	None	Ferrous sulfate	39	3,710	First	Yes[a]
6a	25	None	Folic acid	42	3,640	ND	No
6b	26	None	Folic acid	40	3,180	First	No
7	31	None	Folic acid	41	4,410	First	No
8	29	None	Folic acid, promethazine hydrochloride	39	2,920	First	No
9	27	None	Folic acid, ferrous sulfate	42	3,125	Second	No

ND, No data are available.
[a] Stopped smoking week 17 (Even smoked during a short period during week 25).

TABLE 2. *Maternal and infant lamotrigine concentrations at delivery and postpartum*

Patient number	Lamotrigine dose (mg/day)	Lamotrigine concentrations (μM)				
		Maternal plasma at delivery	Umbilical cord blood	Infant plasma 24 h after birth	Infant plasma 48 h after birth	Infant plasma 72 h after birth
1	800	15	14	14	12	11
2	650	13	8	—[a]	—[a]	—[a]
3	250	6	8	8	7	5
4	200	18	17	8	7	8
5	600	10	12	10	—[a]	8
6a	300	3	4	5	4	—[a]
6b	300	8	7	8	7	8
7	100	4	4	—[a]	—[b]	2
8	500	6	5	—[b]	—[a]	4
9	250	5	6	8	8	4

[a] Data missing.
[b] Insufficient quantity.

~0.2–1 mg/kg/day, assuming a daily milk intake of 150 ml/day/kg. This corresponds to 9% (median, range 2–20%) of the weight-adjusted maternal daily dose. Median LTG plasma concentrations of the nursed infants were ~30% (range, 23–50%) of the maternal LTG concentrations. No adverse effects were reported in the infants.

DISCUSSION

We have systematically studied LTG pharmacokinetics during delivery, in the neonate, and during lactation in a series of patients treated with LTG. The results showed limited interindividual variation, and the main findings were (a) a slow elimination of LTG in the newborn, (b) a marked change in maternal LTG pharmacokinetics after delivery, (c) a considerable transfer of LTG over the placenta, and (d) an extensive passage of LTG into breast milk.

LTG is metabolized mainly in the liver by glucuronidation and excreted renally as a glucuronide conjugate (2). The metabolism is catalyzed by uridine diphosphate-glucuronosyltransferase (UDPGT), which belongs to a supergene family of enzymes with several isoforms. The isozymes differ but overlap in substrate specificity and regulation (6). Factors known to influence glucuronidation in humans include age, smoking, diet, concomitant drugs, ethnicity, disease state, genetics, and hormones (6). The capacity to glucuronidate has been shown to be reduced in the neonate, and many compounds eliminated by glucuronidation have markedly prolonged $T_{1/2}$ in the neonate (7,8). The conjugates also can be expected to have longer $T_{1/2}$ because of the immature renal function in newborns. The glucuronidation of many drugs reaches its full capacity between the third and fourth years of life (8).

The capacity to eliminate LTG follows a similar age-dependent pattern. Our present observations of a minor decline in LTG concentrations in the infants over 72 h after delivery may indicate that the capacity of the newborn to eliminate LTG is low, in accordance with results obtained for other drugs eliminated by glucuronidation. It should, however, be recognized that the LTG concentrations of the neonates may have been influenced by drug intake through breast milk, although breast-feeding seldom is fully established at this early stage after delivery.

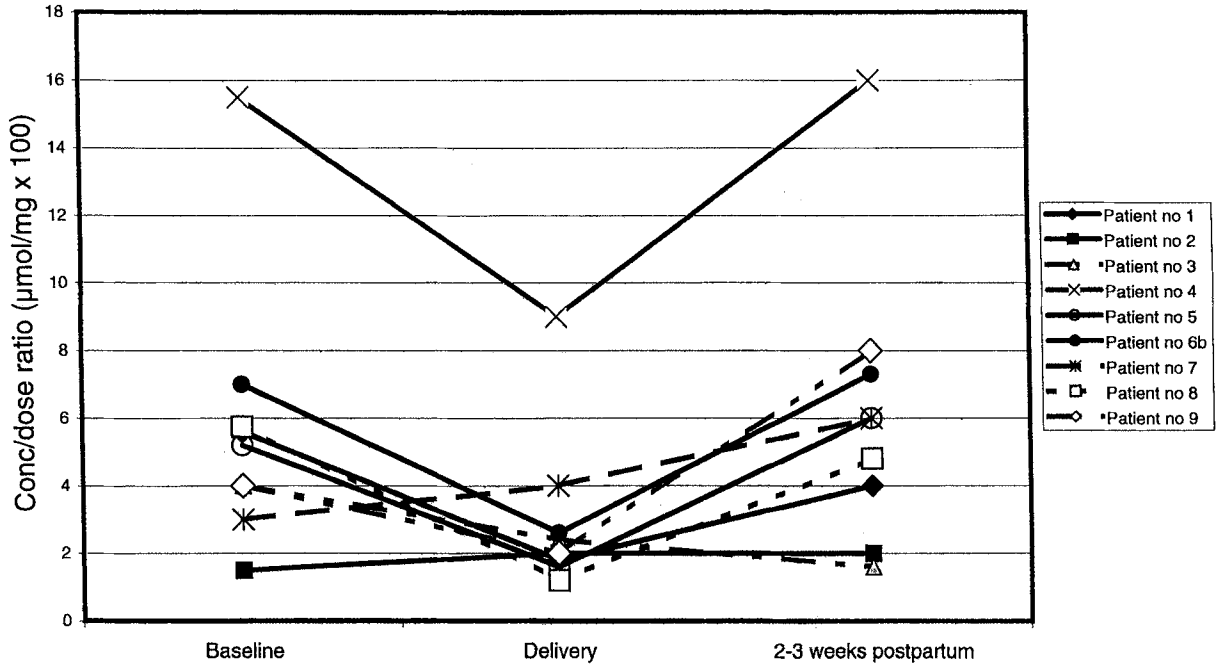

FIG. 1. Lamotrigine concentration/dose ratios at baseline, partus, and during nursing two-three weeks postpartum.

TABLE 3. *Lamotrigine concentration and milk/plasma concentration ratios at time of breast-feeding 2–3 weeks after delivery*

Patient number	Lamotrigine dose (mg/day)	Time of sampling (days after delivery)	Time between last dose and sampling before nursing (h)	Time between last dose and sampling after nursing (h)	Lamotrigine concentration (μM)						Ratios			
					Mother's plasma		Breast milk		Nursed infant's plasma		Milk/ maternal plasma		Infant plasma/ maternal plasma	
					Before nursing	After nursing	Before nursing	After nursing	Before nursing	After nursing	Before nursing	After nursing	Before nursing	After nursing
1	800	16	11.5	12.5	32	32	20	20	10	10	0.62	0.47	0.30	0.30
2	700	13	10.8	1.5[a]	13	27[a]	8	16[a]	3	4[a]	0.61	0.58	0.23	0.15[a]
5	250	15	13.5	14.8	4	4	2	2	2	<2	0.50	0.50	0.50	—
4	200	16	11.3	13.0	29	34	17	17	10	10	0.59	0.50	0.35	0.29
3	600	15	12.4	13.4	40	32	25	21	10	—[b]	0.62	0.66	0.25	—
6a	300	14	—[c]	—[c]	22	22	14	13	5	6	0.64	0.59	0.23	0.27
6b	300	14	10.8	11.5	22	21	13	10	6	7	0.59	0.48	0.27	0.33
7	100	18	12.1	13.1	6	6	4	4	2	<2	0.66	0.66	0.35	—
8	500	15	12.3	13.6	26	22	13	12	13	8	0.50	0.55	0.50	0.36
9	250	17	11.4	12.5	17	22	13	11	6	6	0.77	0.55	0.35	0.27

[a] The dose was administered during nursing.
[b] Insufficient quantity.
[c] The sample was collected as a trough value (exact time for evenings dose not known).

A pronounced increase in maternal serum concentration of LTG after delivery was observed in eight of the cases. This marked alteration probably represents a normalization of the clearance of LTG after pregnancy, as the LTG concentrations/dose ratios 2–3 weeks postpartum did not significantly differ from the baseline values. The clearance of some other drugs that undergo glucuronidation has been shown to be altered during pregnancy. Hence, acetaminophen glucuronidation is markedly induced during pregnancy (6,9), and studies of oxazepam metabolism suggest a shorter half-life in pregnant than in nonpregnant women (10).

Patients 2 and 3, in whom LTG levels did not increase after delivery, were treated with LTG in combination with PHT or CBZ, drugs known to induce the metabolism of LTG (11,12). A reasonable interpretation is therefore that in these cases, the metabolism of LTG was already fully induced by the concomitantly used drugs, and pregnancy had little additive effect on the clearance of LTG.

A considerable transfer of LTG over the placenta is demonstrated by a ratio between the drug concentration in cord blood and maternal plasma close to unity. This corroborates the observations from the two previous case reports (3,4) and is similar to what has been found for other AEDs (13).

The passage of LTG into breast milk is fairly extensive. As a result of this, and of the apparently limited elimination capacity, LTG serum concentrations in the nursed infants were 23–50% of the corresponding concentrations in their mothers. In several cases the serum concentrations of the infants reached levels in the same range as those in many patients taking LTG for therapeutic purposes (14). The intake of LTG of the infant through breast milk was estimated at ~0.5–1 mg LTG/kg/day. However, this figure represents a minimal exposure because the sampling was done before maternal intake of the morning LTG dose. The rising LTG levels in the mothers after delivery may further increase the LTG load to the infant during the first weeks of breast-feeding, unless the LTG doses are reduced. The infant LTG levels obtained 2 weeks after birth may in fact not represent steady-state concentrations, and an extended follow-up period would be of interest in future studies. Our observations point to the need for careful monitoring of the nursed child for adverse effects, although none was noted in this study. In conclusion, our results demonstrate the importance of collecting pharmacokinetic data on the new AEDs to obtain a better basis for rational use of these drugs during pregnancy and after delivery.

Acknowledgment: This study was supported by a grant from the Swedish Medical Research Council (K97-17X-12225-01A) and Glaxo Wellcome. We thank Drs. Jaan Albo, Björn Borre, Jan Calissendorf, Folke Johansson, Jörgen Kinnman, Sven Pålhagen, Richard Schnell, and Birgitta Söderfeldt for contributing their patients to this study.

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