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Levetiracetam Concentrations in Serum and in Breast Milk at Birth and during Lactation

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Summary: *Purpose:* To study the pharmacokinetics of levetiracetam (LEV) at birth, during lactation, and in the nursed infant.

Methods: Eight consecutive breast-feeding women with epilepsy treated with LEV twice daily and their infants were studied.

Results: The mean umbilical cord serum/maternal serum ratio was 1.14 (range, 0.97–1.45) (n = 4). The mean milk/maternal serum concentration ratio was 1.00 (range, 0.76–1.33) at 3 to 5 days after delivery (n = 7). At sampling 2 weeks to 10 months after delivery (n = 5), it was similar (range, 0.85–1.38). At 3 to 5 days after delivery, the infants had very low LEV serum concentrations (<10–15 μM), a finding that persisted during continued breast-feeding. No malformations were detected, and in none of the infants did signs of adverse effects develop.

Conclusions: Our data indicate an extensive transfer of LEV from mother to fetus and into breast milk. However, breast-fed infants had very low LEV serum concentrations, suggesting a rapid elimination of LEV. **Key Words:** Levetiracetam—Lactation—Drug concentration—Epilepsy.

Levetiracetam (LEV) is a new antiepileptic drug (AED) currently approved worldwide for add-on treatment of partial-onset seizures in adults with epilepsy. Its use increases rapidly, and a growing number of women will receive LEV during pregnancy and lactation. Knowledge about the pharmacokinetics in these situations is necessary for adequate counseling of these women. Data are available for older and some of the newer AEDs, but are very limited for LEV (1–5).

LEV is the active, water-soluble (*S*) enantiomer of a racemic pyrrolidine acetamide, chemically unrelated to other AEDs. It is minimally protein bound, and its volume of distribution is close to the volume of intracellular and extracellular water. Sixty-six percent of the dose is renally excreted unchanged. The major metabolic pathway (24% of the dose) is an enzymatic hydrolysis of the acetamide group. It is not dependent on the hepatic cytochrome P-450 system, and therefore LEV is unlikely to be involved in clinically important interactions. The formation of this main metabolite occurs in a wide variety of tissues, including blood cells. The elimination half-life in plasma is 6–8 h, independent of comedication with other AEDs. The metabolites have no known pharmacologic activity and are also renally excreted (6). Reproductive studies in rodents (7) and anecdotal reports of women using LEV in pregnancy (8) have been encouraging. However, care should be taken in extrapolating animal data to humans.

The purpose of the present study was to investigate the human pharmacokinetics of LEV at birth, during lactation, and in the nursed infants.

METHODS

Eight consecutive breastfeeding women with epilepsy treated with LEV twice daily and their infants were studied, seven at delivery and/or postpartum, and one exclusively after 10 months. In four cases, blood samples were obtained at parturition from the mothers and from the umbilical cord. Drug fasting blood samples (10–12 h after last dose) and breast milk (foremilk) were collected concomitantly at various occasions during breast-feeding. Milk/maternal serum concentrations were calculated at 3 to 5 days, and 2, 4, and 6–8 weeks postpartum in most cases, and in two mothers also after 4 and 10 months, respectively. Blood samples were drawn from the infants during breast-feeding at the same intervals before maternal intake of the morning dose. In addition to LEV, two women received carbamazepine (CBZ), one received topiramate (TPM) and valproate (VPA), one lamotrigine (LTG), and one gabapentin (GBP). Two patients received LEV monotherapy (Table 1). One breast-feeding woman receiving VPA and oxcarbazepine (OXC) had started

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TABLE 1. *Patient characteristics*

Patient no.	Age at delivery (yr)	LEV dose (mg/day)	Comedication	Dose (mg/day)
1	35	1,500	Carbamazepine	1,200
2	36	3,500	Carbamazepine	600
3	21	2,000	Valproate	1,800
			+ topiramate	300
4	29	2,500	Lamotrigine	200
5	24	2,000	–	–
6	28	3,000	–	–
7	31	2,500	Gabapentin	1,200

LEV, levetiracetam.

treatment with LEV 9 months after delivery. Blood samples from the mother and the child as well as a milk sample were obtained 4 weeks after LEV was initiated. All infants, except the baby at 10 months, were solely breast-fed.

LEV concentrations in serum and breast milk were measured by an isocratic liquid chromatographic method (9). Chromatograms were run at 35°C, and the column eluent was monitored at 220 nm. The coefficient of variation calculated from between-batch precision of spiked concentrations was 5.0% and 5.9% at 50 μM and 300 μM, respectively. The limit of quantification was 10 μM. The samples were analyzed as part of our daily therapeutic drug-monitoring service as soon as they were received.

RESULTS

The mean umbilical cord serum/maternal serum ratio in four mothers was 1.14 (range, 0.97–1.45), suggesting extensive transplacental transport of LEV. The mean milk/maternal serum concentration ratio (n = 7) was 1.00 (range, 0.76–1.33) at 3 to 5 days after the delivery (Table 2). The mean milk/maternal serum concentration ratios at sampling 2 (n = 5), 4 (n = 2), 6 to 8 weeks (n = 4), and 4 and 10 months (n = 2) after delivery were similar (1.10, 1.14, 1.22, 0.93, and 1.05, respectively). Three to 5 days after delivery, six of the infants had very low LEV serum concentrations (<10–15 μM), and also during follow-up of breast-feeding. One infant had a LEV concentration of 77 μM at day 1, but <10 μM at day 4. One infant with full breast-feeding had a low LEV serum concentrations for 8 weeks (15–17 μM), and <10 μM after 4 months.

The infants exposed to LEV had a mean birth weight of 3,650 g (range, 2,970–4,220 g) and appeared to be healthy throughout the study.

DISCUSSION

Our data suggest that an extensive transfer of LEV occurs from mother to fetus and into breast milk. However, breast-fed infants had very low LEV serum concentrations, suggesting a rapid elimination of LEV, even though reduced absorption in the neonate cannot completely be excluded. No malformations in the infants were detected, and none of them did signs of adverse effects develop.

In one single case report of a woman receiving LEV, the breast milk concentration was 99 μM (10) 7 days after delivery. The milk/maternal serum ratio was 3.09. The serum concentration in the infant was not measured, but the baby became increasingly hypotonic and drank with more difficulty. It was discharged healthy 10 days after the mother had stopped breast-feeding. This unusual high excretion into breast milk is not in accordance with our findings of a more equal distribution between serum and breast milk.

The infants in our study had very low serum concentrations a few days after parturition and also during prolonged breast-feeding. This is in contrast to reports on serum concentrations of LTG in babies of nursing mothers treated with this drug. As opposed to LEV, LTG is metabolized mainly in the liver by glucuronidation. The capacity of this metabolic pathway is reduced in the neonate and may result in serum concentrations comparable to those found during active LTG treatment (11–13).

TABLE 2. *Levetiracetam concentrations at delivery and postpartum (μM)*

	At delivery			3–5 days after delivery				Ratio breast milk/maternal serum				
Patient no.	Maternal serum	Umbilical cord serum	Ratio umbilical cord/ maternal serum	Maternal serum	Breast milk	Infant serum	Ratio breast milk/ maternal serum	2 wk	4 wk	6–8 wk	4 mo	10 mo
1	–	–	–	37	28	<10	0.76	1.38	1.28	0.95	–	–
2	284	322	1.13	68	71	<10	1.04	0.99	–	1.67	–	–
3	67	97	1.45	69	68	<10	0.99	–	–	–	–	–
4	114	111	0.97	62	58	15	0.94	0.85	0.99	1.04	0.93	–
5	–	–	–	28	30	<10	1.07	1.04	–	–	–	–
6	–	–	–	175	153	77 (1 day)	0.87	–	–	–	–	–
“				124	–	<10 (4 days)						
7	117	117	1.00	86	114	<10	1.33	1.24	–	1.21	–	–
8	–	–	–	–	–	–	–	–	–	–	–	1.05

Conversion factor F, 5.88 (μM, 5.88 × μg/ml).

Unfortunately, we were not able to synchronize the timing of blood samples better in our subjects. The higher maternal as well as umbilical LEV concentrations at delivery were conceivably due to non–drug-fasting conditions (Table 2). The high concentration of 77 μM at day 1 in one infant was measured only few hours after delivery and does probably not reflect exposure through breast milk. Polytherapy also represents a limitation in this study; only two mothers received LEV as the only drug. However, no pharmacokinetic interactions between LEV and these other drugs are known (6). Furthermore, the single sample of drug-fasting breast milk does not fully account for the full course of breast milk excretion/infant exposure throughout a day.

In conclusion, LEV readily crosses the placenta and is excreted into breast milk. Breast-fed infants usually have very low LEV serum concentrations, probably due to a rapid elimination of LEV. Women with epilepsy should in general be encouraged to nurse their infants. Treatment with LEV is no exception.

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