IS BREAST MILK THE BEST FOR BABIES OF MOTHERS ON LEVETIRACETAM?

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

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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, 0.761.33) at 3–5 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 3–5 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.

COMMENTARY

Treating women with epilepsy during reproductive years requires constant reassessment, not only of the efficacy and tolerability of the prescribed medication(s), but also of the potential risks of fetal and neonatal exposure to the regimen. Epilepsy is one of the most common disorders that requires continuous treatment during pregnancy with agents that are potential teratogens. The degree of risk for development of fetal anticonvulsant syndrome (i.e., major congenital malformations, minor anomalies, microcephaly, cognitive dysfunction, intrauterine growth retardation, and infant mortality) is related to the specific medication used and may be proportional to the degree of exposure. Major malformations are known to be a teratogenic risk of antiepileptic drug (AED) exposure during the first trimester. However, other risks of exposure, such as intrauterine growth retardation and cognitive dysfunction, continue throughout pregnancy. Moreover, cognitive development can be influenced by drug exposure throughout gestation and postpartum via medications passed through breast milk.

One method of quantifying fetal exposure to a teratogen is to measure umbilical cord concentrations of the agent at delivery. Previous studies have demonstrated complete transplacental passage of the older AEDs; limited studies of the newer AEDs indicate similar extensive transplacental transfer for lamotrigine, oxcarbazepine, topiramate, and zonisamide (1). Although the study by Johannessen and colleagues is restricted to just four pairs of blood samples from mothers and their infants' umbilical cords at parturition, it is the first report of this kind for levetiracetam (LEV). The mean umbilical cord/maternal serum ratio of 1.14 (range, 0.97–1.45) demonstrates complete transplacental passage of LEV, a ratio not unlike other AEDs.

The benefits of breast-feeding are numerous and include reduced infant mortality, fewer infectious diseases, and decreased risk of immunologically mediated disorders, such as type 1 diabetes mellitus. Breast-feeding has even been linked to enhanced cognitive development (2). Current recommendations are that, in the absence of contraindications, women should breast-feed their infants for at least the first 12 months of life. Any decision to limit breast-feeding must be justified by the fact that the risk to the baby clearly outweighs the benefits of nursing. Unfortunately, this practical directive will never be supported by data obtained through randomized, controlled trials. What is the risk to babies who nurse while their mother is taking medication, and what is the specific risk among different AEDs? Anticipated risks include rash, hepatic dysfunction, hematologic disorders, and immediate CNS side effects, such as lethargy, poor suck,

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and reduced feeding, with slow growth; in addition, long-term neurocognitive development may be effected.

The amount of exposure to a medication through lactation is determined by the amount of drug excreted into breast milk. A common measurement used to assess AED exposure is the milk/maternal plasma ratio of the drug concentration. Studies of many older AEDs indicate low-to-moderate excretion into breast milk with milk/maternal plasma ratios of 0.1–0.6. Limited reports of the breast milk/maternal plasma ratios for lamotrigine, topiramate, and zonisamide vary between 0.41 and 0.93 (1). A more accurate way to estimate the level of drug exposure over time is to measure its concentration in breast milk and multiply that amount by the amount that the infant will ingest (typically, 150 cc/kg/day). A common arbitrary cutoff for a safe value is set at $\leq$10% of the therapeutic dose for infants.

Current recommendations regarding infant safety are to use caution with administering phenobarbital, ethosuximide, and primidone to lactating women, as levels of exposure to infants respectively are estimated at 100%, 50%, and >10% of the weight-adjusted therapeutic dose (2). Sedation has been reported with phenobarbital. In contrast, the estimated levels of exposure for carbamazepine, phenytoin, and valproic acid are 3–5% of the therapeutic dose, standardized by weight, and are considered acceptable medications for women who are breast-feeding (2,3). Interestingly, in spite of these seemingly low exposure levels, adverse events, such as hepatic dysfunction (carbamazepine), methemoglobinemia (phenytoin), and thrombocytopenia and anemia (valproic acid), have been reported with breast-fed infants. Estimates of lamotrigine excretion are approximately 10% of the therapeutic dose (2).

LEV is structurally dissimilar to other AEDs. Many of its physicochemistry properties, however, render it ideal for easy passage into breast milk, including minimal protein binding, low molecular weight, and high lipophilicity (4). A single case report of a woman on LEV detailed a concentration of 99 μM, which is a milk/maternal plasma ratio of 3.09 (5). The newborn was described as hypotonic and having difficulty nursing. This inordinately high excretion of drug into breast milk with deleterious consequences could be used to discourage women on LEV from breast-feeding.

The study by Johannessen et al. measured spot, trough breast foremilk samples (10–12 hours after last dose). The mean milk/maternal serum concentration ratios for seven samples was 1.00 (range, 0.76–1.33) at 3–5 days after delivery, with similar values as far out as 10 months' postpartum. The breast milk concentrations of LEV varied considerably. Even by taking the highest breast milk concentration in this report, the estimated level of exposure to the medicine in these infants is 3.9 mg/kg/day, well within the $\leq$10% safe value. Pediatric studies have reported LEV average doses of 32–50 mg/kg/day (6). One study of infants aged 2 days to 21 months, used doses of 14–144 mg/kg/day. Thus, Johannessen et al. report breast milk concentrations values that fall within the recommended safe exposure index.

Truly remarkable are the low infant serum concentrations reported by Johannessen and colleagues: $\leq$17 μM at 3 days–4 months of life, with the majority of measurements <10 μM. Various factors could contribute to the low concentration levels, including efficient renal excretion, poor oral absorption, or perhaps enhanced enzymatic hydrolysis of the acetamide group. The study does not separate out these factors. However, low serum concentration is the most relevant measure of drug exposure in breast-fed infants, overriding any other calculation. LEV avoids the concerns associated with other AEDs of inefficient elimination in newborns that results from immature hepatic metabolic pathways (e.g., glucuronidation with lamotrigine). These findings with LEV are reassuring regarding the safety of the nursing infants.

However, accurate exposure levels of LEV to breast-fed infants may not actually have been obtained from this study because of several limitations. Measurement of breast milk in the first 3–5 days postpartum can be misleading, as the content is primarily colostrum. By the end of the first week, the milk is mature. Drug penetration is usually higher during the colostral period but is offset by the relatively low volume of milk of 30–100 mL per day. Johannesen et al. did report similar breast milk/maternal serum ratios for LEV concentration as far out as 10 months postpartum.

Accurately forecasting the level of drug exposure to the infant also necessitates consideration of two well-described excretion gradients: distribution gradient and time gradient over 24 hours. Distribution gradient concerns drug concentration from foremilk to hindmilk. Because of the increased lipid content of hindmilk, CNS-active drugs are customarily more concentrated in the hindmilk. The study by Johannessen and colleagues measured only spot foremilk samples and only at drug fasting conditions of 10–12 hours after the last dose. Infant blood samples were drawn at the same time as trough drug concentrations. The timing when the blood was drawn is important to providing an accurate analysis of infant exposure to the drug. Given that the half-life of LEV is only 6–8 hours, the reports of breast milk and infant serum LEV concentrations in this study may significantly underestimate exposure.

Another safety concern for infants is the development of idiosyncratic drug reactions, such as rash or organ failure. The overall decreased risk of idiosyncratic reactions to LEV exposure would suggest that it may be relatively safer for nursing infants. All of the eight infants were described as appearing healthy, although the exact methods by which these children were followed are not clear; however, it is unlikely that blood counts, metabolic profiles, and growth were tracked. More studies are needed to clarify whether lethargy or difficulty feeding needs to be monitored, as previously indicated in a case report (5).

The report by Johannessen et al. provides important preliminary information regarding breast-fed infants exposed to LEV, indicating that LEV may not confer a substantially higher risk than other AEDs and that "the risk to the baby (does not) clearly outweigh the benefits of nursing" (2). Although the study provides limited information, it is an important step toward understanding the fetal and newborn exposure to LEV though transplacental passage and breast milk. Future studies will be needed to clarify the teratogenic risk for major malformations and the long-term neurocognitive consequences of intrauterine and infant exposure to LEV. LEV may offer women the option of giving their infants the medical and psychosocial benefits of breast-feeding.

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