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Levetiracetam

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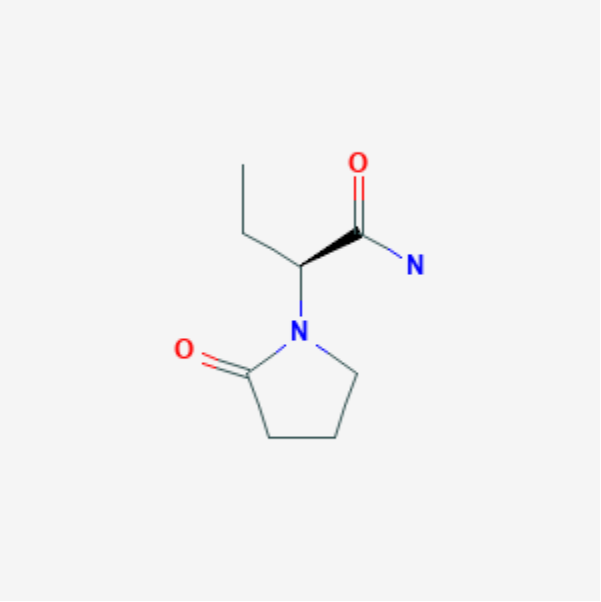

Drug Levels and Effects

Summary of Use during Lactation

Maternal doses of levetiracetam up to 3500 mg daily produce low levels in milk and would not be expected to cause any adverse effects in breastfed infants, especially if the infant is older than 2 months. If levetiracetam is required by the mother, it is not a reason to discontinue breastfeeding. However, the infant should be monitored for drowsiness, adequate weight gain, and developmental milestones, especially in younger, exclusively breastfed infants and when using combinations of anticonvulsants. Maternal serum level monitoring and dosage adjustment is advisable in the early postpartum period if the drug was taken throughout pregnancy and breastfeeding.[1] Some evidence suggests that levetiracetam might reduce the maternal breastmilk supply in some women.

Drug Levels

In published reports of anticonvulsant use during breastfeeding, most women were taking a combination of anticonvulsants. Some other anticonvulsants (e.g., phenytoin, carbamazepine) stimulate the metabolism of other drugs including anticonvulsants, whereas others (e.g., valproic acid) inhibit the metabolism of other drugs. Therefore, the relationship of the maternal dosage to the concentration in breastmilk can be quite variable, making calculation of the weight-adjusted percentage of maternal dosage less meaningful than for other drugs in this database.

Maternal Levels. A woman who was taking phenytoin, valproic acid and an unspecified dosage of levetiracetam had a milk levetiracetam level of 16.9 mg/L 3 hours after a dose, which was 3.1 times her simultaneous serum level.[2]

Breastmilk levels in 12 mothers who were monitored at 4 days and 2 to 3 months postpartum were "significantly lower" than maternal blood levels. Further details were not published in the abstract.[3]

Seven women taking an average of 2430 mg daily (range 1500 to 3500 mg daily) of levetiracetam plus various other anticonvulsants for epilepsy at the time of delivery had foremilk levels measured 3 to 5 days postpartum. Average milk levels were 12.5 mg/L (range 4.8 to 26 mg/L). Milk levels were again measured in 5 of the women plus another woman at one or more of the following times: 2, 4, 6 to 8 weeks and 4 or 10 months postpartum. Specific milk levels were not reported at those times, but the milk to plasma ratio was very similar at those times to the values at 3 to 5 days postpartum.[4]

Eleven mothers who were 4 to 23 days postpartum and taking levetiracetam provided milk samples before nursing. Three women taking 100 mg daily had an average milk levetiracetam concentration of 8.68 mg/L (range 5.79 to 10.55 mg/L); 2 women taking 2000 mg daily had milk levels of 11.7 and 35.7 mg/L; 4 women taking 2500 mg daily had an average milk levetiracetam concentration of 13.95 mg/L (range 10 to 20.4 mg/L); and 2 women taking 3000 mg daily had milk concentrations of 17.4 and 29.1 mg/L. The authors estimated that a fully breastfed infant would receive 7.9% of the maternal weight-adjusted dosage.[5]

A pregnant woman was treated with levetiracetam 1000 mg and lacosamide 100 mg twice daily as well as enoxaparin and labetalol for the rest of her pregnancy and postpartum. Levetiracetam was undetectable (<3 mg/L) in a milk sample on day 5 postpartum (exact time not specified).[6]

A postpartum woman was receiving levetiracetam 3000 mg daily. Milk concentrations ranged from 29 to 51.7 mg/L. Fluctuations in milk concentrations are low, so timing of breastfeeding would have little effect. The authors estimated that an exclusively breastfed infant would receive about 25 to 35 mg daily or about 50% of a therapeutic dose for a 4 kg infant.[7]

Infant Levels. An infant (aged approximately 1 to 2 weeks) of a mother taking phenytoin, valproic acid and levetiracetam (dosage unspecified) had a serum levetiracetam level of 1 mg/L 96 hours after the mother discontinued breastfeeding.[2]

Seven breastfed infants whose mothers were taking an average dosage of 2430 mg daily (range 1500 to 3500 mg daily) of levetiracetam plus various other anticonvulsants during pregnancy and lactation had serum levetiracetam measured before the mother's morning dose at 3 to 5 days of age. In 6 infants, levetiracetam was undetectable (<1.7 mg/L), although one of them had a serum level of 13 mg/L at the age of 1 day. A seventh infant who was fully breastfed had a serum level of 2.5 mg/L at 3 to 5 days of age. This infant and had serum levels ranging from 2.5 to 2.9 mg/L during the first 8 weeks of life and an undetectable serum level at 4 months of age.[4]

Ten infants who were 4 to 23 days old were breastfed by mothers taking levetiracetam in dosages of 1000 to 3000 mg daily. Infant plasma levels were obtained 30 to 120 minutes after nursing and before their mother's morning

dose (10 to 15 hours after the last evening dose), except for one infant whose plasma was sampled before nursing. The average levetiracetam plasma concentration was 1.9 mg/L (range 0.7 to 3.4 mg/L). The infants' plasma levels averaged 13.5% of the maternal plasma concentration taken before their morning dose. The authors found that 13 newborns' levetiracetam elimination half-life averaged 18 hours, which is 2 to 3 times that of adults.[5]

The 10-day-old breastfed (extent not stated) infant of a mother who was taking levetiracetam 3000 mg daily had a serum concentration of 2.1 mg/L, which was less than half of the low end of the therapeutic range. Timing of the sample was not stated.[8]

In a multicenter study of nursing mother-infant pairs, 58 infants had blood samples taken at about the same time as maternal blood samples. Only 18 of the infants had blood levels of lamotrigine above the lower limit of quantification (1.8 mg/L). The authors estimated the average infant lamotrigine serum concentration to be 0.9 mg/L (range 0.9 to 4.5 mg/L), assuming unquantifiable serum concentrations to be 50% of the lower limit of quantification. Median infant blood levels were 5.3% (range 2.1 to 20.4%) of their mothers' blood levels.[9]

Effects in Breastfed Infants

An woman with epilpesy took phenytoin and valproic acid during pregnancy. She began breastfeeding on day 3 postpartum and had a seizure on day 7 postpartum. Levetiracetam (dosage not reported) was started and the infant became increasingly hypotonic and nursed poorly. Breastfeeding was discontinued and the infant was discharged from the hospital in a healthy condition.[2]

Seven exclusively breastfed infants whose mothers were taking an average dosage of 2430 mg daily (range 1500 to 3500 mg daily) of levetiracetam plus various other anticonvulsants during pregnancy and lactation appeared healthy to the investigators throughout the 6 to 8 week study period. An eighth partially breastfed infant whose mother was taking valproate and oxcarbazepine started taking levetiracetam 9 months postpartum appeared healthy at 10 months of age.[4]

No adverse effects were reported in 10 newborns who were 4 to 23 days old who were breastfed during maternal intake of levetiracetam 1000 to 3000 mg daily. Four mothers were also taking lamotrigine; 1 was taking carbamazepine; and one was taking tiagabine, clobazam and oxcarbazepine.[5]

A woman with long-standing seizure disorder was taking primidone and levetiracetam became pregnant. The dosage of her medications were reduced during pregnancy to provide a levetiracetam serum concentration of 40.5 mg/L and a primidone (phenobarbital) serum concentration of 3.4 mg/L. The mother was instructed to discontinue breastfeeding after 3 days. The following day her infant developed withdrawal seizures. After reinstituting breastfeeding, the infant's seizures stopped and did not recur. The infant had no abnormal findings and was thriving and seizure free at 6 months of age.[10]

The infants (including 3 preterm) of 18 nursing mothers who were taking levetiracetam and called the Pharmacovigilance Center in Lyon, France before breastfeeding were paired with 18 control infants. The median dosage was 1000 mg daily (range 500 to 3000 mg daily) and 8 were receiving at least one additional anticonvulsant. The median duration of breastfeeding was 40 days (range 10 to 224 days), and 13 newborns were exclusively breastfed. Breastfed infants were followed for a median of 9.1 months (range 0.75 to 73 months). One 25-day-old infant whose mother was taking levetiracetam 3000 mg daily plus clobazam was hospitalized for sedation, vomiting, and weight loss, and improved rapidly after breastfeeding discontinuation. Another infant exposed to levetiracetam and clobazam had poor weight gain, but it appeared to be caused by poor milk production. Other than these infants, all levetiracetam and control infants grew and developed normally.[8]

A pregnant woman suffered blood clots in the sinuses and 2 small intracranial hemorrhages followed by status epilepticus at 8 weeks of gestation. She was treated with levetiracetam 1000 mg and lacosamide 100 mg twice

daily as well as enoxaparin and labetalol for the rest of her pregnancy and postpartum. Her infant was delivered at 36 weeks gestation and about 50% breastfed for the first days of life. The infant was sleepy and fed poorly, but pauses in breastfeeding did not improve the infant's condition. Breastfeeding was discontinued at 15 days postpartum and the infant gradually improved. The infant showed normal development at 7 months of age.[6]

A mother with epilepsy took levetiracetam 2000 mg daily plus lacosamide 200 mg twice daily while breastfeeding their infants. She breastfed (extent not stated) her infant for 7 months with no infant adverse effects at 24 months of age.[11]

Fourteen nursing mothers were taking an average of 2517 mg daily. Nine infants were fully breastfed and 5 were partially breastfed. The authors reported that no adverse effects were noted in any of the infants.[12,13]

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Effects on Lactation and Breastmilk

In a study of mothers taking levetiracetam during breastfeeding, 7 of 18 mothers discontinued or reduced breastfeeding because of poor milk output. The infant of one mother taking 3000 mg of levetiracetam daily plus clobazam had poor weight gain at day 15 of life.[8]

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Substance Identification

Substance Name

Levetiracetam

CAS Registry Number

102767-28-2

Drug Class

Breast Feeding

Lactation

Anticonvulsants