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Divalproex

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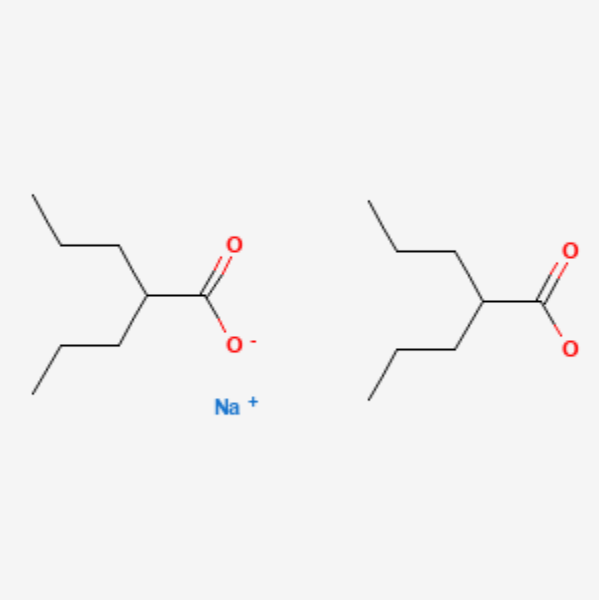
CASRN: 76584-70-8



Drug Levels and Effects

Summary of Use during Lactation

Very little information is available on the clinical use of divalproex during breastfeeding. However, divalproex is rapidly metabolized in the body to the active drug valproic acid. Valproic acid levels in breastmilk are low and infant serum levels range from undetectable to low. Breastfeeding during valproic acid monotherapy does not appear to adversely affect infant growth or development, and breastfed infants had higher IQs and enhanced verbal abilities than nonbreastfed infants at 6 years of age in one study.[1] A safety scoring system finds valproic acid possible to use during breastfeeding.[2] If valproic acid is required by the mother, it is not necessarily a reason to discontinue breastfeeding.

No definite adverse reactions to valproic acid in breastfed infants have been reported. Theoretically, breastfed infants are at risk for valproic acid-induced hepatotoxicity, so infants should be monitored for jaundice and other signs of liver damage during maternal therapy. A questionable case of thrombocytopenia has been reported, so monitor the infant for unusual bruising or bleeding. A rare case of infant baldness might have been caused by valproate in milk. Observe the infant for jaundice and unusual bruising or bleeding. Combination therapy with sedating anticonvulsants or psychotropics may result in infant sedation or withdrawal reactions.

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 mother with epilepsy was taking valproic acid 2.4 grams daily and primidone 250 mg 3 times daily during pregnancy and postpartum. During the second week postpartum, a breastmilk valproic acid level was 7 mg/L, which was 7% of her serum level.[3]

A mother with epilepsy was taking valproic acid 1.6 grams daily in divided doses. The breastmilk level at 5 days postpartum was 7.2 mg/L; by 29 days postpartum, it had fallen to 3 mg/L.[4]

A woman was taking valproic acid 250 mg twice daily during pregnancy and postpartum. At 62 hours postpartum she had a milk level of 0.18 mg/L which was 16 hours after her last dose. At 130 hours postpartum she had a milk level of 0.46 mg/L which was 3 hours after her last dose.[5]

A woman taking valproic acid 250 mg twice daily had milk valproate levels of 2 mg/L 30 minutes after taking a dose. The milk level fell to 0.43 mg/L 1 hour later and to undetectable levels (<0.4 mg/L) an hour after that.[6]

The valproic acid level in the breastmilk of mothers 5 mothers taking valproic acid ranged between 0.4 to 3.9 mg/L. The dosages they were receiving was not stated, but milk levels ranged between 1.3 and 7.1% of the maternal plasma level.[7] This case series was extended to 16 women taking an average of 22.1 mg/kg daily of valproic acid. They had average milk valproate levels of 1.8 mg/L.[8]

In 6 women taking valproic acid in dosages ranging from 9.6 to 31 mg/kg daily, milk valproate levels ranged from 0.034 to 5.4 mg/L and levels of the metabolite 3-keto-valproate ranged from 0.04 to 0.48 mg/L.[9] Extension of the study to 13 patients did not markedly alter the results.[10]

Four women taking valproic acid (1 took 1.2 grams daily and 3 took 1.5 grams daily) had breastmilk valproate levels measured. Specific milk concentrations are not given, but milk levels were 5 to 10% of maternal serum levels, consistent with other studies. The authors estimated that a breastfed infant would receive only 6 mg in a liter of milk.[11]

Four mothers taking valproic acid (3 took 1.2 grams daily and 1 took 1.8 grams daily) during pregnancy and postpartum had breastmilk levels measured during the first week postpartum. The average breastmilk levels were 1.8 mg/L (range 1 to 3.8 mg/L).[12]

One woman taking valproic acid 1 gram daily had milk levels of 3, 2.3 and 1.4 mg/L on postpartum days 6, 7, and 17, respectively. Another woman was taking valproic acid 1.4 gram plus carbamazepine 600 mg and diazepam 2 mg daily. Milk valproate levels were 2, 1.4, 3.5, 2.3 and 2.8 mg/L on postpartum days 1, 3, 15, 29, and 43, respectively.[13]

A case series of 30 patients taking valproic acid reported milk levels collected between day 6 and 32 postpartum (median 7 days), mostly in the morning before the first dose of the day. Seventeen were taking valproic acid monotherapy, with or without clonazepam, in a mean dosage of 11.3 mg/kg daily. Sixteen milk levels that were measured had a mean milk valproate levels of 1.6 mg/L (range <1 to 13.3 mg/L). Three mothers were taking valproic acid plus the enzyme inhibitor lamotrigine in a mean dosage of 11.2 mg/kg daily. Two milk levels that were measured had milk valproate levels <1 mg/L. Nine were taking valproic acid plus an enzyme-inducing drug in a mean dosage of 14.6 mg/kg daily. Ten milk levels that were measured had a mean milk valproate level of 2.1 mg/L (range <1 to 16.7 mg/L). No correlation was observed between the maternal serum levels and milk levels measured at the same time.[14]

Infant Levels. The breastfed infant of an epileptic mother who was taking valproic acid 1.6 grams daily in divided doses had serum valproic acid level of about 7.5 mg/L on day 5 of life that fell to undetectable levels by day 29.[4]

A 2-month-old breastfed infant was nursed by a mother taking valproic acid 250 mg twice daily. Infant serum levels were undetectable (<0.3 mg/L) before nursing and reached a peak of 14 mg/L 30 minutes after nursing which was 2 hours after the mother's dose. The serum level fell to 7 mg/L 1.5 hours later.[6]

The infant of a mother who was taking valproic acid monotherapy 600 mg twice daily had a serum valproic acid level of 6.6 mg/L at 3 months of age.[15]

Two infants were studied whose mothers were taking valproic acid monotherapy for bipolar disorder. A 1-month-old infant had a serum valproate level of 4 mg/L during maternal therapy with 750 mg daily in divided doses. Another fully breastfed 3-month-old whose mother was taking 250 mg of valproic acid twice daily had a serum level of 1 mg/L.[16]

Two breastfed infants whose mothers were taking valproic acid 500 mg daily for bipolar disorder had undetectable (<3.5 and <5 mcg/L) serum valproate levels. Both mothers were also taking clonazepam; one was also taking trifluoperazine and the other was taking fluoxetine.[17]

Four exclusively breastfed infants whose mothers began taking valproic acid monotherapy postpartum in dosages of 750 or 1000 mg daily had average serum levels of 1 mg/L which averaged 1.8% of their mothers' serum levels. Another infant that was 80% breastfed during maternal treatment with 1 gram daily had a serum level of 0.7 mg/L or 1% of the maternal serum level. A sixth infant that was 50% breastfed during maternal treatment with 1 gram daily had a serum level of 0.7 mg/L or 1.2% of the maternal serum level. All infant serum levels were taken between 4 and 19 weeks of age.[18]

A case series of 30 women taking valproic acid had their infants' serum valproate levels measured between day 6 and 32 postpartum (median 7 days), mostly in the morning before the first dose of the day. The extent and timing of breastfeeding were not reported. Seventeen mothers were taking valproic acid monotherapy, with or without clonazepam, in a mean dosage of 11.3 mg/kg daily. Eighteen infant serum levels that were measured had a mean of 3.7 mg/L (range <1 to 11.6 mg/L), with a mean ratio of maternal to infant serum level of 0.1. Three mothers were taking valproic acid plus the enzyme inhibitor lamotrigine in a mean dosage of 11.2 mg/kg daily. Four infant serum levels that were measured had a mean of 4.5 mg/L (range <1 to 6.6 mg/L), with a mean ratio of maternal to infant serum level of 0.12. Nine mothers were taking valproic acid plus an enzyme-inducing drug in a mean dosage of 14.6 mg/kg daily. Eleven infant serum levels that were measured had a mean valproate level of 5.1 mg/L (range <1 to 17.5 mg/L), with a mean ratio of maternal to infant serum level of 0.14. No correlation was observed between the maternal serum levels and infant serum levels measured at the same time.[14]

In a multicenter study of nursing mother-infant pairs, 2 infants had blood samples taken at about the same time as maternal blood samples. Neither of the infants had blood levels of valproic acid above the lower limit of quantification (15 mg/L). The authors estimated the average infant valproic acid serum concentration to be 7.5

mg/L, assuming unquantifiable serum concentrations to be 50% of the lower limit of quantification. Median infant blood levels were 17.2% (range 12.4 to 22%) of their mothers' blood levels.[19]

Effects in Breastfed Infants

A mother with epilepsy was taking valproic acid 2.4 grams daily and primidone 250 mg 3 times daily during pregnancy and postpartum. During the second week postpartum, her breastfed infant was sedated. Breastfeeding was stopped and the drowsiness cleared.[3] The sedation was possibly caused by primidone in breastmilk although valproic acid might have contributed by increasing primidone levels.

Petechiae, thrombocytopenia, anemia, and mild hematuria occurred in a 2.5-month-old breastfed infant whose mother was taking valproic acid 600 mg twice daily. Blood hemoglobin and reticulocytes normalized between 12 and 19 days after discontinuing breastfeeding. The petechiae resolved 35 days after discontinuing breastfeeding and the infant's platelet count had almost reached the normal range by this time. By day 83, the infant's platelet count was well within the normal range. The authors believed the adverse effect to be caused by valproic acid in breastmilk.[15] However, other authors believe that these symptoms were more likely caused by idiopathic thrombocytopenic purpura following a viral infection.[18]

Two breastfed infants aged 1 and 3 months whose mothers were taking valproic acid monotherapy 750 and 500 mg daily developed normally and had no abnormal laboratory values. Their plasma levels were 6% and 1.5% or their mother's serum levels, respectively.[16]

Six breastfed infants whose mothers were taking valproic acid 750 or 1000 mg daily had no adverse reactions to valproic acid in breastmilk.[18]

An exclusively breastfed infants whose mother was taking valproate 1.8 g, topiramate 300 mg, and levetiracetam 2 g, daily during pregnancy and lactation appeared healthy to the investigators throughout the 6- to 8-week study period.[20]

In a long-term study on infants exposed to anticonvulsants during breastfeeding, no difference in average intelligence quotient at 3 years of age was found between infants who were breastfed (n = 11) a median of 6 months and those not breastfed (n = 24) when their mothers were taking valproate monotherapy.[21] At 6 years of age, extensive psychological and intelligence testing found that the breastfed infants had higher IQ values than the nonbreastfed infants.[1]

A prospective cohort study in Norway followed infants of mothers who took antiepileptic drugs during pregnancy and lactation and compared them to infants of mothers with untreated epilepsy and infants with fathers who took antiepileptics as control groups. Of the 223 mothers studied, 27 were taking valproate monotherapy. Infants were assessed at 6, 18 and 36 months of age. Continuous breastfeeding in children of women using antiepileptic drugs was associated with no greater impaired development than those with no breastfeeding or breastfeeding for less than 6 months.[22,23]

A woman with bipolar disorder who delivered twins and was taking sodium valproate in a therapeutic dosage was started on quetiapine 200 mg and olanzapine 15 mg at 11 pm daily after 20 days postpartum. She withheld breastfeeding during the night and discarded milk pumped at 7 am. She then breastfed her infants until 11 pm. The mother continued feeding the infants on this schedule for 15 months. Monthly follow-up of the infants indicated normal growth and neither the pediatricians nor the parents noted any adverse effects in the infants.[24]

The 4-month-old breastfed infant of a mother taking divalproex for bipolar disorder developed patchy hair loss. The extent of nursing and dosage of divalproex were not stated. Divalproex was discontinued and 2 months later, the infant's hair was normal.[25] The hair loss was possibly caused by valproate.

Effects on Lactation and Breastmilk

Relevant published information was not found as of the revision date.

Alternate Drugs to Consider

(Bipolar Disorder) Lithium, Olanzapine, Quetiapine, Risperidone, Valproic Acid; (Migraine Prophylaxis) Erenumab, Metoprolol, Nortriptyline, Propranolol, Rimegepant, Topiramate, Valproic Acid; (Seizure Disorder) Carbamazepine, Gabapentin, Lamotrigine, Oxcarbazepine, Phenytoin, Valproic Acid

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Substance Identification

Substance Name

Divalproex

CAS Registry Number

76584-70-8

Drug Class

Breast Feeding

Lactation

Milk, Human

Anticonvulsants

Antimanic Agents

GABA Agents