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Primidone

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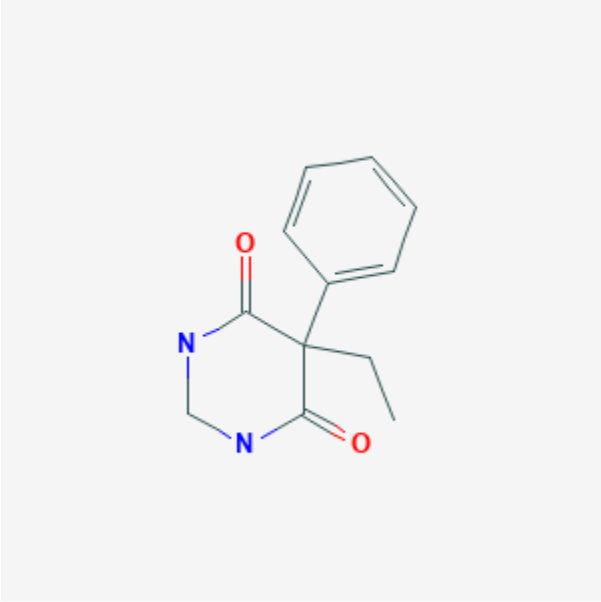
CASRN: 125-33-7



Drug Levels and Effects

Summary of Use during Lactation

Ample evidence exists that primidone taken during nursing can affect the breastfed infant. Infant serum levels of primidone and its metabolites are often near or in the therapeutic range and symptoms of sedation and poor nursing have been reported. On the other hand, infants exposed in utero sometimes have withdrawal symptoms that are either alleviated by breastfeeding or worsened when breastfeeding is abruptly stopped. If primidone is required by the mother, it is not a reason to discontinue breastfeeding. However the infant must be monitored for drowsiness, adequate nursing and weight gain, and developmental milestones, especially in younger, exclusively breastfed infants and when using combinations of anticonvulsant drugs. Measurement of an infant serum level might help rule out toxicity if there is a concern.

Drug Levels

Primidone is metabolized to phenobarbital and phenylethylmalonamide (PEMA) which have sedating and anticonvulsant properties. 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. An epileptic mother was taking primidone 250 mg 3 times daily and valproic acid 2.4 grams daily during pregnancy and postpartum. During the second week postpartum, a breastmilk primidone level was 6 mg/L, which was 50% of her serum level. Primidone metabolites were not measured.[1]

Twelve primidone breastmilk levels were measured between days 3 and 32 postpartum at unstated times after the dose in an unstated number of women who were taking primidone and other anticonvulsants in unstated dosages. Primidone levels averaged 2.3 mg/L (range 0.8 to 2.8 mg/L), while maternal serum levels averaged 2.8 mg/L.[2]

An epileptic woman was taking primidone 1 gram daily and carbamazepine 1 gram daily during pregnancy and postpartum. At 5 weeks postpartum, a milk sample was measured. The milk fat contained 11 mg/L while the skimmed portion contained 9.1 mg/L of primidone. At the same time, phenobarbital levels in milk fat and skimmed milk were 11.2 and 11.4 mg/L, respectively.[3]

Four mothers taking an average dosage of 7.3 mg/kg daily of primidone had breastmilk levels measured of primidone and its metabolites at various times during days 4 to 27 days postpartum. One of the mothers was also taking valproic acid. Average milk levels were as follows: primidone 4.2 mg/L, PEMA 2 mg/L, and phenobarbital 2.8 mg/L. One mother also had 3 hydroxyphenobarbital levels averaging 0.3 mg/L reported.[4] Using the total of all the drug and metabolite levels, an exclusively breastfed infant would receive an average of 18.5% of the maternal-weight-adjusted dosage.

Infant Levels. An infant whose epileptic mother was taking primidone 625 mg, phenobarbital 100 mg, phenytoin 200 mg and sulthiame 200 mg daily during pregnancy and postpartum was partially breastfed. At 17 days of age, the phenobarbital serum level was 2 mg/L. The proportion of breastfeeding was increased, and at 1 month of age, the infant's serum phenobarbital level was 12.7 mg/L. Breastfeeding continued, but by 2 months of age, the serum phenobarbital concentration was 1 mg/L.[5]

The mother of a fully breastfed infant was taking primidone 825 mg daily at birth; dosage was decreased in steps to 625 mg daily at 14 days postpartum and then to 325 mg daily at 1 month of age. The infant's steady-state levels were primidone 2.5 mg/L, PEMA 1.4 mg/L and phenobarbital 10 mg/L during this time. Another mother taking primidone 500 mg daily during pregnancy and breastfeeding. The infant's steady-state levels were primidone 0.7 mg/L, PEMA 0.4 mg/L and phenobarbital 2 mg/L during the first 30 days postpartum.[6]

In a series of 9 mothers who were taking primidone (dosages not reported) during the first week postpartum, the average milk level was 8.4 mg/L (range 5.2 to 13.7 mg/L) which averaged 115% (range 44 to 228%) of their serum levels. Five of the mothers had phenobarbital levels milk levels measured. Milk levels averaged 6.6 mg/L or 37% of their serum levels.[7]

Effects in Breastfed Infants

An infant death occurred from overlying and suffocation by a parent during sleep. Sedation from primidone, phenobarbital and phenytoin in breastmilk was possibly a contributing factor. Phenobarbital was found in the infant's serum (8 mg/L) and liver (16 mcg/g) on autopsy.[8]

An epileptic mother was taking primidone 250 mg 3 times daily and valproic acid 2.4 g daily during pregnancy and postpartum. During the second week postpartum, her breastfed infant was sedated. Breastfeeding was stopped and the drowsiness cleared.[1] The sedation was possibly caused by primidone in breastmilk.

A woman taking primidone 1 g daily and carbamazepine 1 g daily during pregnancy and postpartum breastfed her infant for 5 weeks and noted no difference in the infant's activity before and after nursing.[3]

A probable case of drug-induced drowsiness occurred in a newborn whose mother was taking primidone, carbamazepine and phenytoin (dosages not stated). At day 30, breastfeeding was discontinued because of the drowsiness that occurred after each feeding and poor weight gain. These authors also found that 15 partially breastfed infants whose mothers were taking anticonvulsants, including primidone, gained weight at a slower rate during the first 5 days postpartum than did 75 infants of epileptic mothers who bottle fed or control mothers taking no medications.[9]

Possible drug-related drowsiness, pallor and feeding difficulties were reported in a 4-day-old whose mother was taking primidone 625 mg, phenobarbital 100 mg, phenytoin 200 mg and sulthiame 200 mg daily during pregnancy and postpartum. Nasogastric feeding was required for 5 weeks, during with time the infant continued to be partially breastfed.[5]

In a cohort study of women who were taking primidone during pregnancy and their infants, 7 infants had withdrawal symptoms after birth. Of these infants, one was partially breastfed and the rest were not breastfed. In contrast, five infants who were breastfed did not have withdrawal symptoms.[6]

Sedation lasting 5 weeks after birth and a lack of weight gain for 4 weeks after birth were reported in the exclusively breastfed infant of a mother who was taking primidone 11.4 mg/kg daily, valproic acid 13.6 mg/kg daily, and ethosuximide 11.4 mg/kg daily during pregnancy and postpartum.[10] The reaction was possibly caused by primidone in breastmilk.

A breastfed infant whose mother was taking primidone 375 mg, phenobarbital 90 mg, and carbamazepine 800 mg daily did well despite a saliva phenobarbital level of 3.4 mg/L. At 7 months of age, after the mother abruptly stop nursing, the infant had a number of "startle reactions"and infantile seizures occurred which were confirmed by an abnormal electroencephalogram. Continued phenobarbital administration to the infant for 15 months controlled the seizures and no more occurred up to 5 years of age.[11]

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 primidone (phenobarbital) serum concentration of 3.4 mg/L and a levetiracetam serum concentration of 40.5 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.[12]

Effects on Lactation and Breastmilk

No direct effect is known, but mothers taking antiepileptic drugs stop breastfeeding earlier and supplement more than mothers not taking antiepileptic drugs. Most of these reports occurred in older studies in which sedating agents such as phenobarbital and primidone were used. Infant sucking difficulties and sedation were reasons given for the reduced nursing.[9][13]

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Substance Identification

Substance Name

Primidone

CAS Registry Number

125-33-7

Drug Class

Breast Feeding

Lactation

Anticonvulsants

Barbiturates