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Phenobarbital

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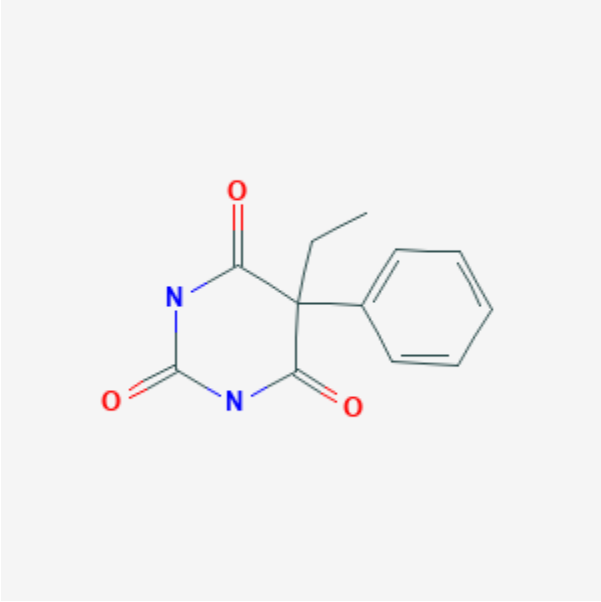

Drug Levels and Effects

Summary of Use during Lactation

Inter- and intrapatient variability in excretion of phenobarbital into breastmilk is extensive. Phenobarbital in breastmilk apparently can decrease withdrawal symptoms in infants who were exposed in utero, but it can also cause drowsiness in some infants, especially when used with other sedating drugs. Monitor the infant for drowsiness, adequate weight gain, and developmental milestones, especially in younger, exclusively breastfed infants and when using combinations of psychotropic drugs. Sometimes breastfeeding might have to be limited or discontinued because of excessive drowsiness and poor weight gain. If there is concern, measurement of the infant's serum phenobarbital concentration might help rule out toxicity.

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. In women taking phenobarbital for 3 days, average milk levels at 23 hours after the last dose were as follows: 90 mg daily in 4 women, 0.85 mg/L (range 0.8 to 1 mg/L); 150 mg daily in 2 women, 1.25 mg/L (range 1 to 1.5 mg/L); 225 mg daily in 2 women, 5.2 mg/L (range 2.7 to 5 mg/L). The same paper reported 2 women taking phenobarbital 125 mg 3 times daily along with phenytoin. Milk phenobarbital levels were fairly constant during the day, averaging from 5.6 to 6 mg/L at 6 am, 10 am and 8 pm in one woman between days 3 and 7 postpartum. In the other, milk levels averaged 7.3, 7.8 and 8.8 mg/L at 6 am, 10 am and 8 pm, respectively, between days 5 and 11 postpartum.[1]

A breastmilk phenobarbital level of 2.7 mg/L was found 16 hours after the last dose in a patient taking 30 mg 4 times daily for 3.5 days at 6 days postpartum.[2]

Eight phenobarbital 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 phenobarbital and other anticonvulsants in unstated dosages. Phenobarbital milk levels averaged 10.4 mg/L (range 0.5 to 33 mg/L), while maternal serum levels averaged 19.3 mg/L.[3]

Phenobarbital breastmilk concentrations were determined in a group of 26 mothers with epilepsy who were taking phenobarbital alone or in combination with other anticonvulsants. Determinations were made at 4 times after delivery: within 5 days postpartum, 6 to 10 days postpartum, 1 to 2 months postpartum and 3 to 5 months postpartum. Levels were obtained 2 to 3 hours after the last dose of the day. Between 13 and 18 mothers provided samples in each time period. For each mg/kg of phenobarbital that the mothers took, their breastmilk concentrations increased by about 1 to 2 mg/L with monotherapy and 1.25 to 2.5 mg/L with combination therapy. The difference between monotherapy and combination therapy was statistically significant only during the first 5 days postpartum.[4]

Milk samples were obtained during the first week postpartum from 4 mothers who were taking phenobarbital. Their dosages ranged from 30 to 150 mg daily in 3 divided doses and milk samples were obtained 2 to 3 hours after a dose. Milk concentrations ranged from 4.5 mg/L in a woman taking 30 mg daily to 7.6 mg/L in a woman taking 150 mg daily. Phenobarbital concentrations in milk were less than those in simultaneous maternal serum samples in all cases.[5] Using the values in this paper, the average weight-adjusted infant dosage was 72.5% (range 39 to 135%) of the maternal dosage.

Infant Levels. An infant whose epileptic mother was taking phenobarbital 100 mg, primidone 625 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 infant's serum phenobarbital concentration was 1 mg/L.[6]

Phenobarbital serum concentrations were determined in a group of infants whose mothers were taking phenobarbital alone or in combination with other anticonvulsants. Determinations were made at 4 times after delivery: within 5 days postpartum, 6 to 10 days postpartum, 1 to 2 months postpartum and 3 to 5 months postpartum. Levels were obtained 2 to 3 hours after the last dose of the day. Between 14 and 18 infants provided samples in each time period. The extent of breastfeeding was not reported. For each mg/kg of phenobarbital that

the mothers took, their infants' serum concentrations increased by about 2 to 5 mg/L with monotherapy and combination therapy, except during the first 5 days postpartum when an increase in serum phenoarbital concentration was about 10 mg/L for each mg/kg of the mothers' dose. The difference between monotherapy and combination therapy was statistically significant only during the first 5 days postpartum. This greater serum concentration in the early days postpartum probably reflects transplacental passage to some extent.[4]

The breastfed (extent not stated) infant of a mother who was taking phenobarbital 90 mg daily during pregnancy and postpartum had phenobarbital plasma levels measured on day 6 and 19 postpartum. On day 6, the plasma levels were 12.1 and 28.3 mg/L before and 2.5 hours after the mother's dose, respectively. On day 19, infant plasma levels had increased to 15.4 and 54.7 mg/L before and 2.5 hours after the mother's dose, respectively.[7]

Effects in Breastfed Infants

Two 1-week-old infants whose mothers had been receiving phenobarbital 100 mg at bedtime for 3 to 5 nights exhibited deep slumber with difficulty in awakening that was possibly caused by phenobarbital in breastmilk.[8]

A mother was taking phenobarbital 390 mg daily and phenytoin 400 mg daily during pregnancy and postpartum. Her infant was drowsy at birth, refused to suck and was given partial formula feeding. At 5 days of age, her infant was admitted to the hospital pale and collapsed with bruising, bleeding, and a decreased hemoglobin, thought to be due to methemoglobinemia. Breastfeeding was discontinued and the infant was given a transfusion which rapidly improved her condition. On day 10, the mother resumed breastfeeding the infant. Within 24 hours the infant was extremely sedated and refused to suck and was fed breastmilk with a spoon. The sedation persisted for 2 days until breastmilk was discontinued permanently because of a return of methemoglobinemia. The extreme sedation was probably due to phenobarbital in the milk and the methemoglobinemia was probably caused by the phenytoin.[9]

An infant death occurred from overlying and suffocation by a parent during sleep. Sedation from phenobarbital, primidone, 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.[10]

Probable drug withdrawal symptoms, manifested as spontaneous tremors, occurred in a breastfed infant in the third month of life when her mother who was taking phenobarbital (dose not stated) during pregnancy and breastfeeding, abruptly discontinued nursing.[11]

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 13 partially breastfed infants whose mothers were taking anticonvulsants 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.[12]

A breastfed infant whose mother was taking phenobarbital 90 mg, primidone 375 mg, and carbamazepine 800 mg daily did well despite a phenobarbital saliva 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.[13]

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.[12][14]

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Substance Identification

Substance Name

Phenobarbital

CAS Registry Number

50-06-6

Drug Class

Breast Feeding

Lactation

Anticonvulsants

Barbiturates

Hypnotics and Sedatives

GABA Modulators