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Fosphenytoin

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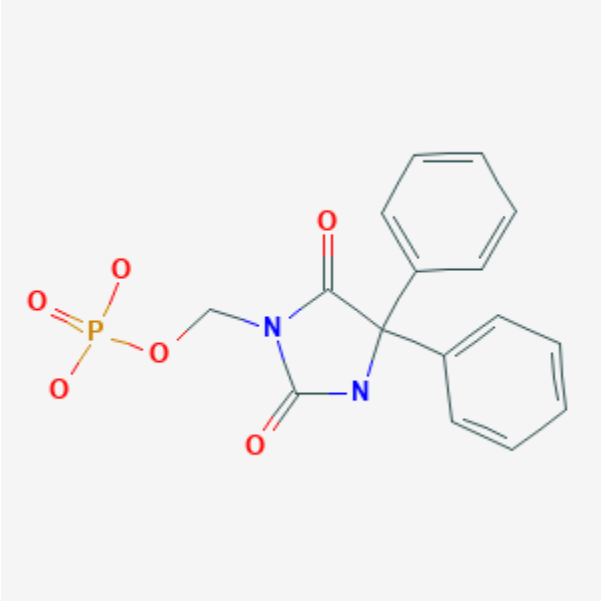

Drug Levels and Effects

Summary of Use during Lactation

No information is available on the clinical use of fosphenytoin during breastfeeding. However, fosphenytoin is rapidly metabolized in the body to the active drug phenytoin. Breastfeeding during phenytoin 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] If phenytoin is required by the mother, it is not necessarily a reason to discontinue breastfeeding.

Because of the low levels of phenytoin in breastmilk, amounts ingested by the infant are small and usually cause no difficulties in breastfed infants when used alone except for rare idiosyncratic reactions. Combination therapy with sedating anticonvulsants or psychotropics may result in infant sedation or withdrawal reactions. In one case report, maternal phenytoin dosage requirements decreased as breastfeeding was discontinued.[2]

Drug Levels

Fosphenytoin is rapidly metabolized to phenytoin, formaldehyde and phosphate after administration. Information on phenytoin during breastfeeding is listed below. 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. Two women were taking phenytoin plus phenobarbital orally. In one woman taking phenytoin 30 mg 3 times daily, milk phenytoin levels were fairly constant during the day, averaging 0.5 mg/L (ranging 0.4 to 0.7 mg/L) at 6 am, 10 am and 8 pm between days 3 and 7 postpartum. In the other woman taking 100 mg 3 times daily, milk levels averaged 0.65, 1 and 1.1 mg/L at 6 am, 10 am and 8 pm, respectively, between days 5 and 11 postpartum.[1]

Two women were taking phenytoin 300 mg daily (dosage details not reported) during pregnancy and postpartum. In one, milk levels ranged from 1.2 to 2.2 mg/L at various times on days 4 to 6 postpartum. The highest levels were reported on day 6. In the other, levels ranged from 1 to 2.6 mg/L on days 1 to 4 postpartum and was 1.3 mg/L on day 33 postpartum.[3]

A woman was taking phenytoin 100 mg 3 times daily. Breastmilk levels varied during the day, with a level of 1.4 mg/L before the first morning dose and a level of 4.2 mg/L 2 hours after the last dose of the day.[4]

In a woman taking phenytoin 500 mg daily in 2 divided doses 12 hours apart, breastmilk phenytoin levels were 0.58 mg/L 3 hours after the morning dose and 0.26 mg/L 1 hour before the evening dose.[5]

A woman usually maintained on phenytoin 300 mg daily was given a single oral dose of 100 mg of phenytoin at 7 am and no other doses on that day. The trough level of 1.2 mg/L from the previous day's dosage occurred one hour after the dose and a peak milk level of 4.5 mg/L occurred 4 hours after the dose. From 1 pm until 8 am the next morning, milk levels fluctuated between 0.5 and 1 mg/L.[6]

Eight phenytoin 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 phenytoin and other anticonvulsants in unstated dosages. Phenytoin milk levels averaged 0.8 mg/L (range 0.5 to 1.4 mg/L), while maternal serum levels averaged 4.5 mg/L[7]

A mother who was taking phenytoin 200 mg twice daily had breastmilk phenytoin levels measured 5 times during days 2 to 4 postpartum. Milk levels ranged from trace to 2 mg/L.[8]

Two mothers taking phenytoin during pregnancy and postpartum had breastmilk levels measured during the first week postpartum. One who was taking 300 mg daily had a milk level of 2.7 mg/L and the other who was taking 200 mg daily had a milk level of 1.7 mg/L[9]

Phenytoin was measured in breastmilk in 5 women. In one taking 100 mg daily, a breastmilk levels of 0.76 mg/L was found 3 days postpartum. In 4 others taking 300 mg daily, milk levels on several occasions mostly during the first week postpartum ranged from 0.41 to 1.3 mg/L. Most of the levels were in the range of 0.5 to 0.6 mg/L.[10] [11]

It is estimated that a breastfed infant would receive between 0.5 and 8% of the maternal weight-adjusted dosage of phenytoin in breastmilk.[12]

Infant Levels. Six breastfed infants whose mothers were taking phenytoin 200 to 400 mg daily had serum phenytoin levels measured between 1 and 3 months of age. Only 2 of the 6 infants were found to have detectable

serum levels during breastfeeding; the levels were 126 and 197 mcg/L. Only 1 infant had a measurable serum level of 4-hydroxyphenytoin of 118 mcg/L.[13]

Effects in Breastfed Infants

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.[14]

One clinician reported that the breastfed infants of 28 mothers who were taking phenytoin 100 to 200 mg 3 times daily had no adverse reactions including drowsiness or lethargy.[15]

No adverse effects were noted in the breastfed neonates of 2 mothers who were taking phenytoin 300 mg daily.[3]

A 10-week-old breastfed infant whose mother was taking clemastine, phenytoin and carbamazepine was drowsy, refused to feed, was irritable, and had high-pitched crying.[16] These side effects were possibly caused by clemastine in breastmilk, but the other drugs could also have contributed.

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. The same group of researchers found that 15 partially breastfed infants whose mothers were taking various anticonvulsants, including phenytoin, 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.[17]

Drowsiness, pallor and feeding difficulties in a 2-week-old were possibly caused by primidone and phenytoin in breastmilk. Possible drug-related drowsiness, pallor and feeding difficulties were reported in a 4-day-old whose mother was taking primidone, phenobarbital, phenytoin and sulthiame.[18] Although phenytoin might have contributed to these outcomes, it is more likely that they were due primarily to the more sedating anticonvulsants, primidone and phenobarbital.

Two breastfed infants (one full, one partial) whose mothers took phenytoin during pregnancy and postpartum became hyperexcitable when their serum phenytoin dropped to unmeasurable levels at 3 to 6 weeks of age.[19]

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 = 17) a median of 6 months and those not breastfed (n = 23) when their mothers were taking phenytoin.[20] At 6 years of age, extensive psychological and intelligence testing found no difference between the breastfed and nonbreastfed infants.[1]

Effects on Lactation and Breastmilk

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

References

1. Meador KJ, Baker GA, Browning N et al. Breastfeeding in children of women taking antiepileptic drugs: Cognitive outcomes at age 6 years. JAMA Pediatr. 2014;168:729-36. PubMed PMID: 24934501.
2. Puckett JB, Butler WM, McFarland JA. Phenytoin and lactation. Arch Neurol. 1982;39:457-8. Letter. PubMed PMID: 7103792.
3. Mirkin BL. Diphenylhydantoin: placental transport, fetal localization, neonatal metabolism, and possible teratogenic effects. J Pediatr. 1971;78:329-37. PubMed PMID: 5539782.
4. Horning MG, Nowlin J, Hickert P et al. Identification of drugs and drug metabolites in breast milk by gas chromatography-mass spectrometry. In: Galli C, Jacini G, Pecile A, eds. Dietary lipids and postnatal development. New York: Raven Press, 1973:257-69.
5. Rane A, Garle M, Borga O et al. Plasma disappearance of transplacentally transferred diphenyl-hydantoin in the newborn studied by mass fragmentography. Clin Pharmacol Ther. 1974;15:39-45. PubMed PMID: 4808742.
6. Horning MG, Stillwell WG, Nowlin J et al. Identification and quantification of drugs and drug metabolites in human breast milk using GC-MS-COM methods. Mod Probl Pediatr. 1975;15:73-9.
7. Kaneko S, Sato T, Suzuki K. The levels of anticonvulsants in breast milk. Br J Clin Pharmacol. 1979;7:624-7. Letter. PubMed PMID: 465285.
8. Soderman P, Matheson I. Clonazepam in breast milk. Eur J Pediatr. 1988;147:212-3. Letter. PubMed PMID: 3366144.
9. Meyer FP, Quednow B, Potrafki A et al. [The perinatal pharmacokinetics of anticonvulsant drugs]. Zentralbl Gynakol. 1988;110:1195-205. PubMed PMID: 3239295.
10. Shimoyama R, Ohkubo T, Sugawara K et al. Monitoring of phenytoin in human breast milk, maternal plasma and cord blood plasma by solid-phase extraction and liquid chromatography. J Pharm Biomed Anal. 1998;17:867-9. PubMed PMID: 9682171.
11. Sugawara K, Shimoyama R, Ohkubo T. Determinations of psychotropic drugs and antiepileptic drugs by high-performance liquid chromatography and its monitoring in human breast milk. Hirosaki Med J. 1999;51(Suppl):S81-6.
12. Bar-Oz B, Nulman I, Koren G et al. Anticonvulsants and breastfeeding. A critical review. Paediatr Drugs. 2000;2:113-26. PubMed PMID: 10937463.
13. Steen B, Rane A, Lonnerholm G et al. Phenytoin excretion in human breast milk and plasma levels in nursed infants. Ther Drug Monit. 1982;4:331-4. PubMed PMID: 7157456.
14. Finch E, Lorber J. Methaemoglobinaemia in the newborn. Probably due to phenytoin excreted in human milk. J Obstet Gynaecol Br Emp. 1954;61:833-4. PubMed PMID: 13222209.
15. Livingston S. Treatment of epilepsy with diphenylhydantoin sodium (Dilantin sodium). Postgrad Med. 1956;20:584-6.
16. Kok TH, Taitz LS, Bennett MJ et al. Drowsiness due to clemastine transmitted in breast milk. Lancet. 1982;319:914-5. Letter. PubMed PMID: 6122135.
17. Kaneko S, Suzuki K, Sato T et al. The problems of antiepileptic medication in the neonatal period: is breast-feeding advisable? In: Janz D, Dam M, Richens A et al. Epilepsy, pregnancy and the child. New York: Raven Press, 1982:343-8.
18. Granstrom ML, Bardy AH, Hiilesmaa VK. Prolonged feeding difficulties of infants of primidone mothers during neonatal period: preliminary results from the Helsinki study. In: Janz D et al., eds. Epilepsy, pregnancy and the child. New York: Raven Press, 1982:357-8.
19. Koch S, Gopfert-Geyer I, Hauser I et al. Neonatal behaviour disturbances in infants of epilepetic women treated during pregnancy. Prog Clin Biol Res. 1985;163B:453-61. PubMed PMID: 3983173.
20. Meador KJ, Baker GA, Browning N et al. Effects of breastfeeding in children of women taking antiepileptic drugs. Neurology. 2010;75:1954-60. PubMed PMID: 21106960.

Substance Identification

Substance Name

Fosphenytoin

CAS Registry Number

93390-81-9

Drug Class

Breast Feeding

Lactation

Anticonvulsants