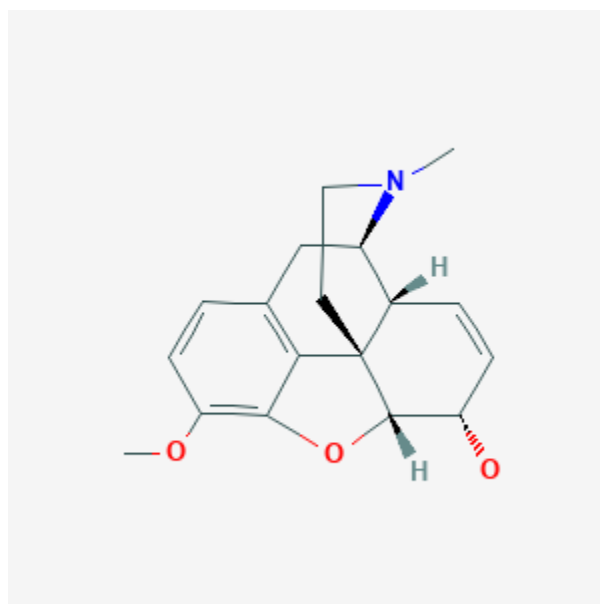




Codeine

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Drug Levels and Effects

Summary of Use during Lactation

Maternal use of codeine during breastfeeding can cause infant drowsiness, central nervous system depression and even death, with pharmacogenetics possibly playing a role.[1][2] Newborn infants seem to be particularly sensitive to the effects of even small dosages of narcotic analgesics. Once the mother's milk comes in, it is best to provide pain control with a nonnarcotic analgesic and limit maternal intake of oral codeine to 2-4 days at a low dosage with close infant monitoring, especially in the outpatient setting.[2][3][4][5] If the baby shows signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness, a physician should be contacted immediately.[6] Excessive sedation in the mother often correlates with excess sedation in the breastfed infant. Following these precautions can lower the risk of neonatal sedation.[7] Numerous professional organizations and regulatory agencies recommend that other agents are preferred over codeine or to

avoid codeine completely during breastfeeding;[8][9][10][11][12] however, other opioid alternatives have been studied less and may not be safer.[13]

Drug Levels

Codeine is metabolized via CYP2D6 to morphine (5%), norcodeine (15%), and further to codeine-6-glucuronide (80%) and morphine-6-glucuronide by UGT2B7. Codeine itself has very weak analgesic activity. The morphine and codeine-6-glucuronide metabolites are responsible for codeine's analgesic properties. Both CYP2D6 and UGT2B7 are subject to genetic variability which can alter the amount of active narcotic excreted into breastmilk. The plasma clearance of morphine is prolonged in newborn infants compared to older infants and children.[2][14]

Maternal Levels. Two mothers who were 7 and 13 weeks postpartum were given a single 60 mg dose of oral codeine. Milk was collected over 12 hours in the first subject and over 48 hours in the second. Codeine and morphine were detected in the milk of both subjects with peak codeine levels in milk occurring 1 hour after the dose. The peak codeine milk level was 455 mcg/L in the first subject and about 450 to 550 mcg/L in the second. The half-life of codeine in breastmilk was 2.5 hours. Morphine milk levels were 16 mcg/L and 9 mcg/L 1 hour after the dose in the 2 subjects. Elimination of morphine from milk occurred very slowly over 36 hours. The authors calculated an average milk level from 0 to 12 hours after a single codeine 60 mg dose to be 140 mcg/L for codeine and 9 mcg/L for morphine. They also estimated an average steady-state codeine milk concentration of 351 mcg/L and morphine milk concentration of 42 mcg/L from a codeine dose of 60 mg every 4 hours.[15] Using the average milk level data from this study, including the contribution of the morphine metabolite, an exclusively breastfed infant would receive an estimated maximum dose of 11 mcg/kg in the 12 hours after a single 60 mg maternal dose and 59 mcg/kg daily from a maternal dosage regimen of 60 mg taken every 4 hours. The amounts of codeine and morphine in milk in this study represent an infant dosage of about 1.2% of the maternal weight-adjusted codeine dosage. The typical neonatal dose of codeine is 500 mcg/kg every 6 to 8 hours. The levels of codeine-6-glucuronide were not measured in this study and thus, results likely underestimate complete infant exposure to active substances in milk from maternal codeine use.

Seven mothers who were 1 to 3 days postpartum and taking codeine 60 mg every 4 to 6 hours for an average of 4 doses had foremilk sampled up to 6 hours after a dose. One mother's serial milk levels at 0.5, 1, 2, and 4 hours after the dose were 71, 71, 199, and 126 mcg/L for codeine and 8.5, 9.1, 11.2, and 12.7 mcg/L for morphine, respectively. Using these levels, a calculated average milk level is 124 mcg/L for codeine and 9.6 mcg/L for morphine. The range of measured milk levels from all subjects was 33.8 to 314 mcg/L for codeine and 1.9 to 20.5 mcg/L morphine. Time to codeine milk level peak was variable. The subject with the highest measured milk codeine level of 314 mcg/L had this measurement 3.5 hours after her fifth dose. One subject had a measurable milk codeine level 35 hours after her twelfth dose.[16][17] Using the calculated average codeine milk level, including the contribution of the morphine metabolite, an exclusively breastfed infant would receive an estimated maximum 20 mcg/kg daily from a maternal dosage regimen of 60 mg taken every 4 hours. This represents an infant dosage of 0.3% of the maternal weight adjusted dosage. Using the peak codeine and morphine milk levels from this study, an exclusively breastfed infant would receive an estimated maximum of 50 mcg/kg daily from a maternal dosage regimen of 60 mg taken every 4 to 6 hours. This represents 1% of the maternal weight-adjusted dosage. The typical neonatal dose of codeine is 500 mcg/kg every 6 to 8 hours. The levels of codeine-6-glucuronide were not measured in this study and thus, results likely underestimate complete infant exposure to active substances in milk from maternal codeine use.

A mother took codeine 60 mg with acetaminophen every 12 hours for 2 days postpartum, then codeine 30 mg every 12 hours for episiotomy pain. A pumped milk sample from day 10 postpartum (time with respect to dose not stated) contained 87 mcg/L of morphine which was several times higher than expected. Genetic analysis revealed that she was heterozygous for CYP2D6*2A with a CYP2D6*2x2 gene duplication classifying her as an ultra-rapid CYP2D6 metabolizer.[18] A follow-up study of nursing mothers who had taken codeine during

nursing found that mothers who reported central nervous system depression during codeine use were more likely to have CYP2D6 duplication and UGT2B7 *2/*2 genotype than those who reported no central nervous system depression.[19]

Infant Levels. Plasma samples from 11 healthy, term, 1- to 3-day-old infants of 11 mothers taking codeine for postpartum analgesia were drawn 1 to 4 hours after completion of breastfeeding. The mothers had taken an average of 4 doses of oral codeine 60 mg every 4 to 6 hours for analgesia prior to infant plasma sampling. One hour after a dose the mean infant serum codeine level was 1.86 mcg/L (range 0.8 to 4.5 mcg/L). At 2 hours the mean was 1.15 mcg/L (range 0.8 to 1.5 mcg/L). At 4 hours the mean was 1.4 mcg/L (range of 0.8 to 3.3 mcg/L). Mean infant serum morphine levels were 0.86 mcg/L at 1 hour, 0.58 mcg/L at 2 hours and 0.8 mcg/L at 4 hours. The morphine to codeine ratio was higher in infant serum than in milk, possibly due to conversion of codeine to morphine in the infants. The authors noted that the infant serum codeine and morphine levels reported in this study are lower than known therapeutic plasma levels reported in adults and neonates treated with codeine or morphine for analgesia.[17] The levels of codeine-6-glucuronide were not measured in this study and thus, results likely underestimate infant exposure to active substances in milk from maternal codeine use.

An author reported two cases. In one, a codeine-dependent mother taking codeine 300 mg daily breastfed (extent not stated) her infant. The infant's urine contained codeine in a concentration of 1 mg/L (sampling time not stated). In the other case, a heroin-dependent mother was taking 625 mg of codeine daily as a replacement. Dihydrocodeine 1.5 mg/L was measured in the infant's serum. The age and extent of nursing were not reported.[20]

Effects in Breastfed Infants

Codeine was reported to be the possible cause of asymptomatic bradycardia 6 days following a 30 mg single maternal codeine dose in a week-old, term, exclusively breastfed infant.[21]

Four probable cases of apnea associated with maternal codeine intake of 60 mg every 4 to 6 hours were reported in 4- to 6-day-old term and near-term breastfed infants. Apnea resolved 24 to 48 hours after withholding breast feeding and discontinuation of maternal codeine.[22]

In a case-control study of 12 breastfed term newborns with unexplained episodes of apnea, bradycardia or cyanosis during the first week of life, maternal oral codeine use was determined to be the probable cause. A higher proportion of newborns with episodes, 83 vs 31%, had mothers using opiates, including codeine, for postpartum analgesia. The mean number of doses taken was also higher with mothers of case newborns taking a mean of 10 doses (range 4 to 22) vs. 5 doses (range 1 to 13) in the control group. There were no differences in other perinatal and demographic factors between cases and controls.[23] The authors recommended discontinuation of breastfeeding if infants of mothers taking opiate analgesics have unexplained negative cardiorespiratory symptoms.

No apnea, bradycardia, or color changes occurred in 11 healthy, term, 1- to 3-day-old newborn breastfed infants exposed to codeine in milk. Their mothers had taken an average of 4 doses of oral codeine 60 mg every 4 to 6 hours prior to breastfeeding.[17]

In one telephone follow-up study, 19% (5 of 26) of breastfeeding mothers taking multiple doses of codeine reported drowsiness in their infants. All infants were younger than 1 month.[24] The authors added that the elimination half-life of codeine's metabolite, morphine, is prolonged in the newborn period which may explain why the adverse reaction was reported in only infants younger than 1 month.

A heroin-dependent mother was taking 625 mg of codeine daily as a replacement. Her infant (age and extent of nursing not stated) was described as cyanotic and apneic.[20]

A large case-control study of 504 children with neuroblastoma found a statistically significant 2.4-fold association of the disease with maternal use of opioid agonists during pregnancy and lactation. This finding was largely attributable to a 3.4-fold association with maternal codeine use. Opioid exposure during lactation had a 3.5-fold association while codeine exposure had a 5.1-fold association. Because neuroblastoma is a sympathetic nervous system tumor arising from the progenitor cells of the sympathetic ganglia and adrenal medulla, and because codeine does cross the placenta and is transferred to milk, the authors of this study speculate that codeine's neuroendocrine effects could disrupt adrenal gland development in the fetus and neonate thus contributing to neuroblastoma.[25]

A breastfed infant became increasingly sleepy and lethargic starting on day 7 of life. The infant developed gray skin and decreased milk intake on day 12 of life and died on day 13 of life. The infant's mother was taking acetaminophen with codeine prescribed for post-episiotomy pain at a codeine dose of 60 mg every 12 hours on days 1 and 2 postpartum, and 30 mg every 12 hours for 2 weeks. The mother was found to be an ultrarapid metabolizer of codeine who excreted very large amounts of morphine into her breastmilk.[18] The authors later conducted a retrospective case-control study of 72 women who had taken codeine while breastfeeding found that 24% of the mothers reported decreased alertness in their infants which improved after codeine or breastfeeding discontinuation. The affected infants were more likely to have visited an emergency room for symptoms such as lethargy, poor feeding or breathing difficulties. Mothers with affected infants took an average of 1.62 mg/kg daily of codeine compared to an average of 1.02 mg/kg daily in mothers of unaffected infants. The lowest maternal dose reported cause symptoms in the breastfed infant was 0.63 mg/kg daily. Usually the mothers of affected infants also had signs of central nervous system depression. Another woman was also an ultrarapid codeine metabolizer in addition to the first case reported. She took 120 mg of codeine daily and her infant was very drowsy and fed poorly and the mother was sedated, nauseated, dizzy, and weak during codeine use. The mother transitioned to complete formula feeding by day 7 postpartum and noted a complete reversal of her infant's symptoms although she remained symptomatic.[26]

A study compared the frequency of drowsiness in breastfed infants whose mothers took acetaminophen plus codeine to infants whose mothers took acetaminophen alone. Infants exposed to codeine had a 16.7% frequency of drowsiness compared to 0.5% of those exposed to acetaminophen alone. Mothers having infants with drowsiness took about 50% higher doses of codeine than those with no drowsiness.[27]

In a retrospective study, nursing mothers who were taking either codeine, oxycodone or acetaminophen for pain while breastfeeding were contacted by telephone to ascertain the degree of maternally perceived central nervous system (CNS) depression. Some of the mothers taking codeine had been previously reported in reference [26]. Mothers taking codeine reported signs of CNS depression in 17% (35/210) of their infants, while those taking acetaminophen reported infant CNS depression in only 0.5% (1/184) of their infants. Women who reported infant sedation were taking 1.4 mg/kg daily of oxycodone, and unaffected were taking 0.9 mg/kg daily. Affected infants had more hours of daily uninterrupted sleep than unaffected infants, and 4 of the affected infants had been taken to the emergency department for lethargy. Thirty of 35 mothers reported that infant sedation ceased with maternal codeine discontinuation. Mothers of affected infants were also more likely to experience lethargy and other side effects than mothers of unaffected infants. Mothers who took oxycodone reported a similar rate of infant sedation (20%) compared to codeine, but the groups were statistically different in parity and postmenstrual age (PMA), with the codeine group having a slightly higher PMA.[28]

A retrospective cohort study of women with publically funded prescription coverage compared 7804 women who filled a codeine prescription within 7 days postpartum to 7804 who did not over a 10-year period. No difference was found in any adverse infant outcomes during the first 30 days of life between the two groups, including hospitalization for various causes.[29] However, study design problems appear to have limited this study, including a lack of knowledge of maternal codeine dosage ingested, timing of codeine ingestion, and extent of nursing.[30]

Six cases of CNS depression in infants breastfed by mothers taking codeine were reported over a 2-year period in Canada. Maternal dosages that were reported were in the range of 2 to 3 mg/kg daily. Infants were all 10 days of age or younger and responded favorably to discontinuation of nursing, discontinuation of maternal codeine or naloxone injection.[30]

A 2-month-old breastfed (extent not stated) infant was noted by the mother to be somnolent and sleeping more than usual for 2 to 3 days. The baby's mother had a total of 4 or 5 tablets of acetaminophen 500 mg plus codeine 30 mg as needed for back pain for the prior 3 days. The mother discontinued the medication and breastfeeding. Under observation at an emergency room, the infant slowly recovered. A serum morphine level was not obtained.[31]

Effects on Lactation and Breastmilk

Narcotics can increase serum prolactin.[31] However, the prolactin level in a mother with established lactation may not affect her ability to breastfeed.

Alternate Drugs to Consider

(Analgesia) Acetaminophen, Butorphanol, Hydromorphone, Ibuprofen, Morphine; (Antitussive) Dextromethorphan

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Substance Identification

Substance Name

Codeine

CAS Registry Number

76-57-3

Drug Class

Breast Feeding

Lactation

Analgesic, Opioid

Narcotics

Antitussive Agents