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Codeine

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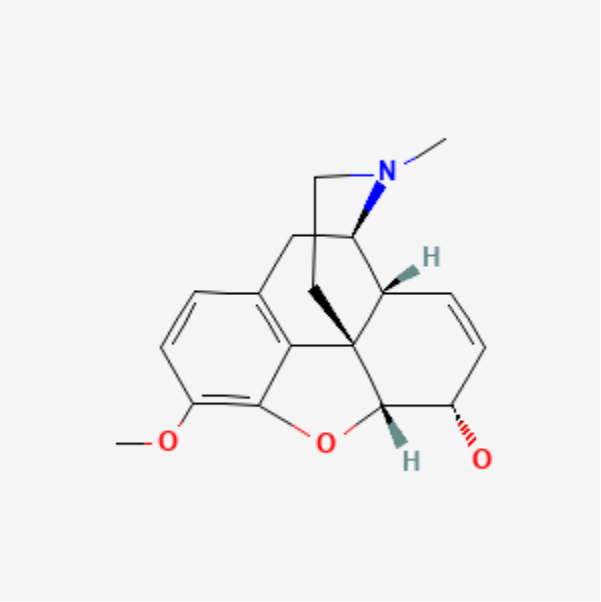

Drug Levels and Effects

Summary of Use during Lactation

Maternal use of oral opioids during breastfeeding can cause infant drowsiness, which may progress to rare but severe central nervous system depression.[1,2] Newborn infants seem to be particularly sensitive to the effects of even small dosages of narcotic analgesics. If codeine is required by the mother of a newborn, it is not a reason to discontinue breastfeeding; however, 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 to 3 days at a low dosage with close infant monitoring, especially in the outpatient setting.[2-4] If the baby shows signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness, a physician should be contacted immediately.[5] Excessive sedation in the mother often

correlates with excess sedation in the breastfed infant. Following these precautions can lower the risk of neonatal sedation.[6] Numerous professional organizations and regulatory agencies recommend that other agents are preferred over codeine or to avoid codeine completely during breastfeeding;[7-11] however, a large population study did not find codeine to be more dangerous than other opioids that have been studied less and may not be safer.[12-14]

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.[2,15]

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.[16] 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.[17,18] 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.[19] 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.[20]

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.[18] 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.

Effects in Breastfed Infants

Codeine was reported to be the possible cause of asymptomatic bradycardia 6 days following a single maternal 30 mg codeine dose in a week-old, term, exclusively breastfed infant.[21] This seems implausible.[13]

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.[18]

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. 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.[24]

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 (although the dose was later reported to be 30 mg every 6 hours[13]). The mother was found to be a ultrarapid metabolizer of codeine who excreted large amounts of morphine into her breastmilk.[18] The role that codeine and its pharmacogenetics played in the infant's death has been questioned and the paper was retracted by two Canadian journals where the case was originally published.[2,13,26,27] The authors of the original case report 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 or 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.[28]

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.[29]

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 previously been reported in reference [28]. 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.[30]

A retrospective cohort study of women with publicly funded prescription coverage in the province of Ontario, Canada 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.[31] 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.[32] In a similar, but larger study in Ontario, 17,037 mothers who filled a codeine prescription were matched on propensity score to an equal number of mothers who did not. Compared with infants born to mothers who were not prescribed an opioid, those born to mothers prescribed codeine were less likely to be admitted to hospital in the 30 days after the index date (hazard ratio 0.74).

Admissions for and feeding difficulties were less common among infants of mothers who filled a codeine prescription than among infants of mothers who did not fill a codeine prescription. No infant deaths occurred. Of note is that the median drug supply was for 3 days (IQR 2-4).[14]

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.[32]

A 2-month-old breastfed (extent not stated) infant was noted by the mother to be somnolent and slept 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.[33]

Effects on Lactation and Breastmilk

Narcotics can increase serum prolactin.[34] 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

References

1. Madadi P, Shirazi F, Walter FG, Koren G. Establishing causality of CNS depression in breastfed infants following maternal codeine use. Paediatr Drugs 2008;10:399-404. PubMed PMID: 18998750.
2. Willmann S, Edginton AN, Coboeken K, et al. Risk to the breast-fed neonate from codeine treatment to the mother: A quantitative mechanistic modeling study. Clin Pharmacol Ther 2009;86:634-43. PubMed PMID: 19710640.
3. Nauta M, Landsmeer ML, Koren G. Codeine-acetaminophen versus nonsteroidal anti-inflammatory drugs in the treatment of post-abdominal surgery pain: A systematic review of randomized trials. Am J Surg 2009;198:256-61. PubMed PMID: 19628064.
4. Ito S. Opioids in breast milk: Pharmacokinetic principles and clinical implications. J Clin Pharmacol 2018;58 (Suppl 10):S151-S163. PubMed PMID: 30248201.
5. US Food and Drug Administration. Public Health Advisory. Use of codeine products in nursing mothers. 2007;Aug 17. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm054717.htm
6. Kelly LE, Chaudhry SA, Rieder MJ, et al. A clinical tool for reducing central nervous system depression among neonates exposed to codeine through breast milk. PLoS One 2013;8:e70073. PubMed PMID: 23922910.
7. Sachs, HC, The Committee on Drugs. The transfer of drugs and therapeutics into human breast milk: An update on selected topics.[Reaffirmed May, 2018]. Pediatrics 2013;132:e796-809 PubMed PMID: 23979084.
8. United States Food and Drug Administration. FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. 2017;April 20. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm

9. Lazaryan M, Shasha-Zigelman C, Dagan Z, Berkovitch M. Codeine should not be prescribed for breastfeeding mothers or children under the age of 12. Acta Paediatr 2015;104:550-6. PubMed PMID: 25809057.
10. European Medicines Agency. Codeine-containing medicines. 2013;EMA/385716/2013. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine-containing_medicines/human_referral_prac_000008.jsp&mid=WC0b01ac05805c516f
11. Lamvu G, Feranec J, Blanton E. Perioperative pain management: An update for obstetrician-gynecologists. Am J Obstet Gynecol 2018;218:193-9. PubMed PMID: 28666699.
12. Halder S, Russell R, Quinlan J. Codeine and breast-feeding mothers. Int J Obstet Anesth 2015;24:5-7. PubMed PMID: 25578245.
13. Zipursky J, Juurlink DN. The implausibility of neonatal opioid toxicity from breastfeeding. Clin Pharmacol Ther 2020;108:964-70. PubMed PMID: 32378749.
14. Zipursky JS, Gomes T, Everett K, et al. Maternal opioid treatment after delivery and risk of adverse infant outcomes: Population based cohort study. Bmj 2023;380:e074005. PubMed PMID: 36921977.
15. Madadi P, Koren G. Pharmacogenetic insights into codeine analgesia: Implications to pediatric codeine use. Pharmacogenomics 2008;9:1267-84. PubMed PMID: 18781855.
16. Findlay JW, DeAngelis RL, Kearney MF, et al. Analgesic drugs in breast milk and plasma. Clin Pharmacol Ther 1981;29:625-33. PubMed PMID: 7214793.
17. Naumburg EG, Meny RG, Findlay J, et al. Codeine and morphine levels in breast milk and neonatal plasma. Pediatr Res 1987;21 (4, Pt 2):240A. doi:10.1203/00006450-198704010-00437
18. Meny RG, Naumburg EG, Alger LS, et al. Codeine and the breastfed neonate. J Hum Lact 1993;9:237-40. PubMed PMID: 8260056.
19. Koren G, Cairns J, Chitayat D, et al. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. Lancet 2006;368:704. PubMed PMID: 16920476.
20. Madadi P, Ross CJ, Pape T, et al. A toxicogenetic case-control study of codeine toxicity during breastfeeding. Clin Pharmacol Ther 2008;83 (Suppl 1s):S2. doi:10.1038/sj.clpt.2008.36
21. Smith JW. Codeine-induced bradycardia in a breast-fed infant. Clin Res 1982;30:259A.
22. Davis JM, Bhutani VK. Neonatal apnea and maternal codeine use. Pediatr Res 1985;19 (4 Pt 2):170A. doi:10.1203/00006450-198504000-00389
23. Naumburg EG, Meny RG. Breast milk opioids and neonatal apnea. Am J Dis Child 1988;142:11-2. PubMed PMID: 3341293.
24. Ito S, Blajchman A, Stephenson M, et al. Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal medication. Am J Obstet Gynecol 1993;168:1393-9. PubMed PMID: 8498418.
25. Cook MN, Olshan AF, Guess HA, et al. Maternal medication use and neuroblastoma in offspring. Am J Epidemiol 2004;159:721-31. PubMed PMID: 15051581.
26. Tsuyuki RT, Pimlott N. Risks of maternal codeine intake in breast-fed infants: A joint statement of retraction from the Canadian Pharmacists Journal and Canadian Family Physician. Can Pharm J (Ott) 2021;154:7-8. PubMed PMID: 33599627.
27. Pimlott N, Tsuyuki RT. Risks of maternal codeine intake in breastfed infants: A joint statement of retraction from Canadian Family Physician and the Canadian Pharmacists Journal. Can Fam Physician 2020;66:793-6. PubMed PMID: 33208416.
28. Madadi P, Ross C, Hayden M, et al. Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: A case-control study. Clin Pharmacol Ther 2009;85:31-5. PubMed PMID: 18719619.
29. Ciszkowski C, Madadi P, Sistonen J, et al. The incidence of CNS depression of neonates breastfed by mothers receiving codeine for postpartum analgesia. Clin Pharmacol Ther 2011;89 (Suppl. 1):S94. doi:10.1038/clpt.2010.335
30. Lam J, Kelly L, Ciszkowski C, et al. Central nervous system depression of neonates breastfed by mothers receiving oxycodone for postpartum analgesia. J Pediatr 2012;160:33-7.e2. PubMed PMID: 21880331.

31. Juurlink DN, Gomes T, Guttmann A, et al. Postpartum maternal codeine therapy and the risk of adverse neonatal outcomes: A retrospective cohort study. Clin Toxicol (Phila) 2012;50:390-5. PubMed PMID: 22537257.
32. Lam J, Matlow JN, Ross CJ, et al. Postpartum maternal codeine therapy and the risk of adverse neonatal outcomes: The devil is in the details. Ther Drug Monit 2012;34:378-80. PubMed PMID: 22777151.
33. Moranta F. [Pharmaceutical enquiry by drowsiness in breastfed baby]. Farmaceuticos Comunitarios 2016;8:42-4. doi:10.5672/FC.2173-9218.(2016/Vol8).004.0610.5672/FC.2173-9218
34. Tolis G, Dent R, Guyda H. Opiates, prolactin, and the dopamine receptor. J Clin Endocrinol Metab 1978;47:200-3. PubMed PMID: 263291.

Substance Identification

Substance Name

Codeine

CAS Registry Number

76-57-3

Drug Class

Breast Feeding

Lactation

Milk, Human

Analgesics, Opioid

Narcotics

Antitussive Agents