# Guidelines for maternal codeine use during breastfeeding

Parvaz Madadi PhD Myla Moretti MSc Nada Djokanovic MD MSc Pina Bozzo
Irena Nulman MD FRCPC Shinya Ito MD FRCPC Gideon Koren MD FRCPC FACMT

**ABSTRACT**

**QUESTION** In light of the recent evidence of adverse events in infants whose mothers use codeine medication, we have been struggling with the issue of how to manage codeine analgesia in our postpartum patients. What are some guidelines for the safe use of codeine during breastfeeding?

**ANSWER** Motherisk has summarized recent scientific evidence into suggested guidelines for the safe use of codeine during breastfeeding.

**RÉSUMÉ**

**QUESTION** Compte tenu des récentes données scientifiques sur les événements indésirables survenus chez des nourrissons dont les mères prenaient des médicaments avec codéine, nous nous demandons comment procéder en ce qui a trait à l'administration postpartum d'analgésiques avec codéine à nos patientes. Existe-t-il des directives sur l'utilisation sans danger de la codéine pendant l'allaitement?

**RÉPONSE** Motherisk a résumé les données scientifiques récentes sous forme de lignes directrices proposées pour l'utilisation sécuritaire de la codéine durant l'allaitement.

It is widely recognized that maternal pain should be managed following delivery, but the issue of how to adequately provide this pain relief has not been resolved. Any medication prescribed during the postpartum period must be safe and effective for mothers without causing harm to breastfed infants. Although there is an absence of scientific data supporting its use,[1] many institutions in North America prescribe the combination of acetaminophen (300 mg), codeine (30 mg), and caffeine (15 mg) (ie, Tylenol No. 3) for analgesia following cesarean section or episiotomy.[2] The rationale for choosing codeine analgesia appears to be institutional tradition and years of experience in the hospital setting. However, mothers rarely have follow-up appointments once discharged from the hospital, and recent evidence of adverse drug reactions in breastfed infants whose mothers are prescribed outpatient codeine medication[3-5] necessitates guidelines in this population (**Boxes 1** and **2**).

## Postpartum use

A review of the pharmacologic mechanism of codeine analgesia sheds light on issues surrounding its postpartum use.[6] Codeine is a prodrug that must be metabolized via the cytochrome P450 2D6 (CYP 2D6) enzyme into morphine to elicit an analgesic effect[7,8]; however, the CYP 2D6 gene is highly polymorphic.[9] While codeine is effective for most individuals worldwide who possess 2 functional copies of the gene, about 8% of Europeans do not possess any active gene copies, and thus are unable to receive analgesia.[10] On the other hand, functional duplications of the CYP 2D6 gene (which range from 2% to 40% of individuals, depending on ethnic background[10]) enhance morphine biotransformation from codeine[11] and have been associated with adverse events,[12,13] including death in a breastfed infant.[4,5] There are commercial tests available for CYP 2D6 genetic screening; however, clinical trials supporting its introduction in the hospital setting have not yet been performed.

While maternal genotype should certainly be considered before codeine is prescribed, patient education might be an equally important preventive

**Box 1. Codeine use during breastfeeding**

A large number of women are treated for pain following cesarean section or episiotomy.

- It is important to effectively treat postpartum pain.
- Codeine is widely used for postpartum pain, mostly in combination with acetaminophen. Tylenol No. 3 is the most common codeine-acetaminophen combination in clinical use.
- Recent research from Motherisk suggests that codeine might not be safe for all breastfed infants, as in a minority of cases it might cause CNS depression and apnea.
- A minority of mothers might convert more codeine to morphine in their bodies, putting their babies at risk of side effects or even death.
- Infants appear to be more sensitive to the effects of narcotic opioids, such as morphine, than older children or adults.

CNS—central nervous system.

**Box 2. Motherisk guidelines for safe use of medications that contain codeine during breastfeeding:** *These guidelines are based on the available scientific data.*

In most cases, the occurrence of CNS depression is consistent between the mother and the baby. If the mother suffers from symptoms of CNS depression (eg, somnolence, grogginess), a physician should examine the baby for signs of CNS depression as well.

- If the baby is not fed well, does not wake up to be fed, does not gain weight, or shows limpness, he or she should be examined by a physician.
- Central nervous system depression in the baby appears to worsen after 4 days, probably owing to the accumulation of morphine with more breastfeeding. If possible, codeine should not be used for longer than 4 days. If pain still necessitates codeine, an attempt should be made to decrease the dose or to switch to non-codeine painkillers (eg, NSAIDs).
- Women who convert more codeine to morphine have a duplication of the gene encoding for cytochrome P450 2D6. This genetic predisposition can be detected by genetic test. This test, although not available in most hospitals, is available on the market.
- Although codeine is widely used in North America, 9 randomized studies comparing the use of codeine with various NSAIDs in laparotomy cases (ie, abdominal surgery) failed to show codeine to be superior in pain relief.

CNS—central nervous system, NSAIDs—nonsteroidal anti-inflammatory drugs.

measure. Newborn infants appear to be most sensitive to the effects of narcotic opioids as compared with older infants[5,14-16]; however, many mothers are unaware of the symptoms of central nervous system (CNS) depression and what to look for in their babies. In any case in which a baby is not fed well, does not wake up to be fed, does not gain weight, or shows limpness, he or she should be examined by a physician. These symptoms tend to appear after 4 days[3,5] of continuous breastfeeding while using codeine and are likely due to the accumulation of morphine in the infant.[17] It follows that higher maternal codeine dose is associated with a higher risk of neonatal adverse events.[3,5] Thus, if pain still necessitates codeine after 4 days, an attempt should be made to decrease the dose or to switch to non-codeine painkillers (eg, non-steroidal anti-inflammatory drugs).[5] There is also a strong correlation between CNS depression in the mother and the breastfed baby,[5] which can serve as a warning flag for mothers; if a mother herself feels groggy or sedated, her baby should be examined by a physician for signs of CNS depression as well.

## Conclusion

As the postpartum length of hospital stay has decreased in Canada,[18] the onus for providing a safe and effective analgesic for maternal outpatient use has increased. The strategy of replacing codeine with another opioid analgesic is troublesome in the absence of safety data and clinical experience. However, if codeine is to remain the first-line treatment of postpartum pain, practitioners, as well as patients, should be educated on its risks.

**Competing interests**
None declared

**References**

1. Nauta M, Landsmeer ML, Koren G. Effectiveness and safety of NSAIDs versus acetaminophen/codeine in the treatment of maternal post partum pain: a systematic review. *Am J Surg* 2009;198:256-61.
2. Peter EA, Janssen PA, Grange CS, Douglas MJ. Ibuprofen versus acetaminophen with codeine for the relief of perineal pain after childbirth: a randomized controlled trial. *CMAJ* 2001;165(9):1203-9.
3. Madadi P, Shirazi F, Walter FG, Koren G. Establishing causality of CNS depression in breastfed infants following maternal codeine use. *Paediatr Drugs* 2008;10(6):399-404.
4. Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* 2006;368(9536):704.
5. Madadi P, Ross CJ, Hayden MR, Carleton BC, Gaedigk A, Leeder JS, et al. Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study. *Clin Pharmacol Ther* 2009;85(1):31-5. Epub 2008 Aug 20.
6. Madadi P, Koren G. Pharmacogenetic insights into codeine analgesia: implications to pediatric codeine use. *Pharmacogenomics* 2008;9(9):1267-84.
7. Chen ZR, Somogyi AA, Reynolds G, Bochner F. Disposition and metabolism of codeine after single and chronic doses in one poor and seven extensive metabolisers. *Br J Clin Pharmacol* 1991;31(4):381-90.
8. Yue QY, Hasselstrom J, Svensson JO, Sawe J. Pharmacokinetics of codeine and its metabolites in Caucasian healthy volunteers: comparisons between extensive and poor hydroxylators of debrisoquine. *Br J Clin Pharmacol* 1991;31(6):635-42.
9. Human Cytochrome P450 *(CYP)* Allele Nomenclature Committee [website]. CYP2D6 *allele nomenclature*. Human Cytochrome P450 *(CYP)* Allele Nomenclature Committee; 2009. Available from: **www.cypalleles.ki.se/cyp2d6.htm**. Accessed 2009 Feb 5.
10. Sistonen J, Sajantila A, Lao O, Corander J, Barbujani G, Fuselli S. CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure. *Pharmacogenet Genomics* 2007;17(2):93-101.
11. Kirchheiner J, Schmidt H, Tzvetkov M, Keulen JT, Lötsch J, Roots I, et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *Pharmacogenomics J* 2007;7(4):257-65. Epub 2006 Jul 4.
12. Gasche Y, Daali Y, Fathi M, Chiappe A, Cottini S, Dayer P, et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *N Engl J Med* 2004;351(27):2827-31. Erratum in: *N Engl J Med* 2005;352(6):638.
13. Dalén P, Frengell C, Dahl ML, Sjöqvist F. Quick onset of severe abdominal pain after codeine in an ultrarapid metabolizer of debrisoquine. *Ther Drug Monit* 1997;19(5):543-4.
14. Way WL, Costley EC, Leongway E. Respiratory sensitivity of the newborn infant to meperidine and morphine. *Clin Pharmacol Ther* 1965;6:454-61.
15. Koren G, Butt W, Chinyanga H, Soldin S, Tan YK, Pape K. Postoperative morphine infusion in newborn infants: assessment of disposition characteristics and safety. *J Pediatr* 1985;107(6):963-7.
16. Bouwmeester NJ, Hop WC, van Dijk M, Anand KJ, van den Anker JN, Tibboel D. Postoperative pain in the neonate: age-related differences in morphine requirements and metabolism. *Intensive Care Med* 2003;29(11):2009-15. Epub 2003 Jul 25.
17. Willmann S, Edginton AN, Coboeken K, Ahr G, Lippert J. Risk to the breast-fed neonate from codeine treatment to the mother: a quantitative mechanistic modeling study. *Clin Pharmacol Ther* 2009. Epub ahead of print.
18. Cargill Y, Martel MJ; Society of Obstetricians and Gynaecologists of Canada. Postpartum maternal and newborn discharge. *J Obstet Gynaecol Can* 2007;29(4):357-63.

## MOTHERISK

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. **Dr Madadi, Ms Moretti, Ms Bozzo,** and **Drs Djokanovic** and **Ito** are members of the Motherisk Program. **Dr Nulman** is Associate Director and **Dr Koren** is Director of the Motherisk Program. **Dr Koren** is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation. He holds the Ivey Chair in Molecular Toxicology in the Department of Medicine at the University of Western Ontario in London.

Do you have questions about the effects of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the Motherisk Program by fax at 416 813-7562; they will be addressed in future **Motherisk Updates**.

Published Motherisk Updates are available on the *Canadian Family Physician* website (**www.cfp.ca**) and also on the Motherisk website (**www.motherisk.org**).