

Safety of codeine during breastfeeding

Fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine

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ABSTRACT

QUESTION Recently a newborn died from morphine poisoning when his mother used codeine while breastfeeding. Many patients receive codeine for postlabour pain. Is it safe to prescribe codeine for nursing mothers?

ANSWER When a mother is an ultrarapid metabolizer of cytochrome P450 2D6, she produces much more morphine when taking codeine than most people do. In this situation, newborns might be exposed to toxic levels of morphine when breastfeeding. Options to reduce this risk include discontinuing codeine after 2 to 3 days of use and being aware of symptoms of potential opioid toxicity in both mothers and newborns.

RÉSUMÉ

QUESTION Un nouveau-né est récemment décédé d'un empoisonnement à la morphine parce que sa mère avait pris de la codéine pendant qu'elle allaitait. De nombreuses patientes reçoivent de la codéine pour les douleurs après le travail. Est-il sécuritaire de prescrire de la codéine aux mères qui allaitent?

RÉPONSE Si la mère métabolise ultra rapidement le cytochrome P450 2D6, elle produit beaucoup plus de morphine lorsqu'elle prend de la codéine que la plupart des autres personnes. Dans une telle situation, un nouveau-né pourrait être exposé à des taux toxiques de morphine quand il est allaité. Pour réduire le risque, on peut, entre autres, cesser l'utilisation de la codéine après 2 ou 3 jours, et demeurer vigilant face aux éventuels symptômes d'une intoxication aux opioïdes chez la mère et le nourrisson.

Codeine is commonly used in the postpartum period for pain associated with episiotomy and cesarean section. As most mothers initiate breastfeeding, the safety of codeine and its pharmacologically active metabolite, morphine, among breastfed infants is of primary concern. The American Academy of Pediatrics and major authoritative texts list codeine as compatible with breastfeeding,^{1,2} despite insufficient published data to support this recommendation. To illustrate the need for further assessment of codeine and morphine transfer into breast milk, we describe a recently published case of a full-term, breastfed infant who died in a manner consistent with morphine overdose.³ Pharmacogenetic assessment of maternal drug biotransformation was consistent with enhanced formation of the pharmacologically active opioid, morphine. To the best of our knowledge, this is the first record of a breastfed baby succumbing to toxicity through breast milk.

Case

A newborn male infant, born after an unremarkable pregnancy and delivery (birth weight 3.88 kg, 90th percentile), developed difficulty breastfeeding and increasing lethargy at 7 days of age. At 11 days of

age, he was taken to a pediatrician owing to concerns about his skin colour and decreased milk intake. The pediatrician noted that the infant had gained his birth weight. Subsequently, on day 13, an ambulance team found the baby cyanotic and without vital signs. Resuscitation, which was initiated at home and continued in the hospital's emergency department, was unsuccessful. Full postmortem analysis failed to identify an anatomic cause of death.

Hepatic steatosis was investigated for medium-chain acyl-CoA dehydrogenase deficiency, which was ruled out. Other fatty acid oxidative disorders, organic acidemias, congenital adrenal hyperplasia, hypothyroidism, and galactosemia were also ruled out. Postmortem toxicologic testing using gas chromatography-mass spectrometry revealed a blood concentration of morphine at 70 ng/mL and acetaminophen at 5.9 µg/mL. Neonates receiving morphine for analgesia have been reported to have serum concentrations of morphine at 10 to 12 ng/mL.⁴

Review of the medical records revealed that in the immediate postpartum period the mother was

prescribed Tylenol® 3 (codeine 30 mg and acetaminophen 500 mg). Initially she took 2 tablets twice daily, but she halved the dose on postpartum day 2 owing to somnolence and constipation. Following the development of poor neonatal feeding, the mother expressed milk and stored it in a freezer. Analysis of the milk for morphine using a specific enzyme-linked immunosorbent assay method for morphine revealed a concentration of 87 ng/mL. At this level, the cross-reactivity of the assay with codeine in our laboratory is less than 4%. The morphine measurement was further confirmed by gas chromatography-mass spectrometry.

Genotype analysis

To address the potential contribution of pharmacogenetic factors to maternal response and neonatal outcome following codeine administration, genotype analysis was conducted for cytochrome P450 2D6 (CYP 2D6), the enzyme catalyzing the O-demethylation of codeine to morphine,⁴ and for uridine diphosphate-dependent glucuronosyltransferase 2B7 (UGT 2B7), the enzyme catalyzing the formation of morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G).⁵

The mother was found to be compound heterozygous for a CYP 2D6*2A allele and a CYP 2D6*2x2 gene duplication. In essence, the mother had 3 functional CYP 2D6 genes and would be classified as an ultrarapid metabolizer. The phenotypic consequence of this genotype is enhanced formation of morphine from codeine, consistent with the symptoms of somnolence and constipation that she experienced with the initial doses of Tylenol® 3. Both the father and the infant possessed 2 functional CYP 2D6 alleles (CYP 2D6*1/*2 genotypes). Both the mother and the infant were homozygous for the UGT 2B7*2 (-161TT, 802TT) allele, which has been associated with increased M6G:morphine compared with the UGT 2B7*1 allele (-161C, 802C).^{6,7} Morphine-6-glucuronide is a highly active metabolite of morphine.

Discussion

The clinical and toxicologic pictures in this case are consistent with opioid toxicity leading to neonatal death. Codeine itself has only mild opioid properties, while most of its analgesia and central nervous system-depressant effects are secondary to its biotransformation to morphine, a reaction catalyzed by CYP 2D6.⁵ While most people are extensive metabolizers of codeine to morphine, CYP 2D6 gene duplication results in an ultrarapid metabolizer phenotype (in an estimated 1% of people in Finland and Denmark, 10% of people in Greece and Portugal, and 29% of people in Ethiopia) and, thus, the potential for substantially increased production of morphine from codeine.⁸ In adults, this has been shown to result in serious opioid toxicity even with small doses of codeine,⁶ an observation consistent with the symptoms of opiate excess

experienced by the mother in this case. Furthermore, the high levels of morphine in the breast milk in this case (86 ng/mL) corroborate the clinical picture observed in the infant. Breastfed infants of mothers prescribed 60 mg of codeine for postnatal pain achieved maximum plasma morphine concentrations of only 2.2 ng/mL.⁷ In our case, a milk sample was available only for a period when the mother halved her dose. Hence, assuming linear kinetics, it is likely that peak levels of morphine in the milk were approximately 100 ng/mL.

The predominant routes of morphine elimination include biotransformation to M3G and M6G. The production of the active metabolite M6G is almost exclusively catalyzed by UGT 2B7.⁹ Sawyer et al¹⁰ reported increased M6G:morphine in individuals homozygous for the single nucleotide polymorphisms constituting the UGT 2B7*2 allele. Since the mother's genotype was UGT 2B7*2/*2, it is possible that the infant might have also been exposed to higher than anticipated concentrations of the pharmacologically active M6G metabolite, and not just of morphine itself.

There are several previous reports of somnolence¹¹ and neonatal apnea¹² in babies exposed to codeine through breast milk, suggesting that varying degrees of opioid toxicity are more prevalent than commonly assumed. Codeine is widely perceived to be compatible with breastfeeding, owing to previously measured low levels of morphine in milk.^{1,2} Our case reveals that polymorphism in CYP 2D6 and possibly UGT 2B7 can be life threatening for some breastfed babies. Given

MOTHE RISK

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. **Dr Koren** is Director and **Drs Karaskov** and **Aleksa** are members of the Motherisk Program. **Ms Madadi** is with the Ivey Chair in Molecular Toxicology at the University of Western Ontario in London. **Dr Cairns** is with the Coroner's Office in Toronto. **Dr Chitayat** and **Ms Teitelbaum** are with Mount Sinai Hospital in Toronto. **Drs Gaedigk** and **Leeder** are with Children's Mercy Hospital in Kansas City, Mo. **Dr Koren** is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation and, in part, by a grant from the Canadian Institutes of Health Research. He holds the Ivey Chair in Molecular Toxicology at the University of Western Ontario.

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 College of Family Physicians of Canada website (www.cfpc.ca) and also on the Motherisk website (www.motherisk.org).

that a CYP 2D6 ultrarapid metabolizer genotype occurs at a frequency of 1% to 29%, genetic combination

Strategies to prevent neonatal morphine toxicity

1. Avoid prescribing codeine and use nonsteroidal anti-inflammatory drugs. This approach might not be possible in cases of severe pain.
2. Prescribe codeine-containing products for 2 to 3 days only, so neonatal accumulation of morphine is prevented.
3. Genotype all postpartum women about to receive codeine. This approach will identify CYP 2D6 and UGT 2B7 genotypes associated with the potential for increased formation of pharmacologically active codeine metabolites, morphine and possibly M6G, and, thus, individuals who are at risk of neonatal toxicity. Currently these tests are not available in most clinical facilities.
4. Carefully follow up all women taking codeine; test both mother and child when mothers are experiencing opioid toxicity.
5. Closely follow up all breastfed infants of codeine-using mothers; test morphine levels whenever there are adverse events consistent with opioid toxicity. In any case where you suspect opioid toxicity, a naloxone test might reverse, and thus corroborate, that toxicity.

would be expected to occur quite commonly among breastfeeding mothers.

As demonstrated by this case, the common practice of prescribing codeine in the postpartum period cannot be regarded as safe for all breastfed infants. Therefore, we propose several clinical approaches that can be considered to prevent life-threatening neonatal toxicity, each with its benefits and disadvantages (see box). Whatever clinical approach is taken, codeine cannot be considered safe during breastfeeding. ❁

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