The Implausibility of Neonatal Opioid Toxicity from Breastfeeding

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The belief that newborns can develop opioid toxicity from breastfeeding is widely held but supported by very little data. Based largely on a single, highly publicized case report (the "Toronto case"), major health agencies worldwide now caution against codeine use by nursing mothers. As a result, "stronger" opioids with greater abuse liability are increasingly prescribed in its place, potentially to the detriment of maternal health. We re-examine aspects of this case report to demonstrate why such an occurrence is highly implausible. The Toronto case involved the death of a 13-day-old infant from opioid toxicity. The child's mother, who took codeine while breastfeeding, was found to have a duplication of *CYP2D6*2*, consistent with ultrarapid metabolizer status. This led to the conclusion that the child died from opioid toxicity due to enhanced maternal conversion of codeine to morphine, with the subsequent passage of large amounts of morphine into breast milk. We argue that this explanation is implausible based upon several factors: (1) the exceedingly small amount of opioids passed into breastmilk irrespective of maternal CYP genotype, (2) the observation that significant neonatal opioid accumulation can only occur in the setting of severely impaired renal function, and (3) the previously unreported finding of a markedly elevated codeine concentration in postmortem blood. Finally, a review of the literature identifies a paucity of convincing reports of neonatal opioid toxicity during breastfeeding, with no other confirmed cases of neonatal death despite the use of these drugs by millions of nursing mothers over the past 2 decades.

The past 2 decades have witnessed a dramatic increase in opioid prescribing, including to women during and after pregnancy. In some jurisdictions, up to 30% of women are prescribed opioids following vaginal delivery, and > 80% receive an opioid following caesarian section.[1] These estimates suggest that hundreds of thousands of women breastfeed while receiving opioids each year in North America alone.

The belief that newborns can develop opioid toxicity from breastfeeding has permeated the medical literature and clinical practice. Codeine in particular has been characterized as unsafe because of its variable and unpredictable conversion to morphine as a consequence of cytochrome P450 2D6 (CYP2D6) pharmacovariants. Concerns about the safety of codeine during breastfeeding have been driven by a few scattered cases—and one fatal case in particular—interpreted as instances of neonatal opioid toxicity resulting from breastfeeding.[2,3] This led the US Food and Drug Administration (FDA), the European Medicines Agency, Health Canada, and the American College of Obstetrics and Gynecology to caution against codeine use by nursing mothers. In its place, "strong" opioids (meaning those generally used at lower milligram doses), such as oxycodone and hydromorphone, are now increasingly prescribed following childbirth.[1,4] This shift in practice may place new mothers at greater risk of persistent opioid use and addiction, and may also pose a hazard to toddlers in the home due to accidental ingestion.[5]

Despite the foregoing, converging lines of evidence indicate that neonatal opioid toxicity from breastfeeding is exceedingly improbable.[6,7] We offer a detailed re-examination of this issue, drawing upon basic principles of pharmacology as well as clinical information not reported in two previous accounts of the case that changed practice.[2,3]

THE CASE THAT SHAPED CURRENT THINKING: THE "TORONTO CASE"

Concerns about the safety of codeine during breastfeeding gained international attention following publication of a case report in 2006.[2] In that report, a full-term male infant weighing 3.88 kg was born to a mother who was prescribed Tylenol with codeine No. 3 (acetaminophen 300 mg, codeine 30 mg, and caffeine 15 mg) for postpartum pain. She initially took 2 tablets twice daily until the second postpartum day, followed by 1 tablet every 6 hours (originally reported in error as twice daily[2,3]). On day 12, the child was noted to be difficult to rouse, appeared grey in color, and exhibited poor breastmilk intake. Paramedics were summoned to the home, and upon arrival found the baby without vital signs. The child was pronounced dead in the hospital shortly thereafter. Postmortem investigation identified no anatomic cause of death but revealed a markedly elevated blood morphine concentration (70 ng/mL). The child was determined to have died of opioid toxicity.

THE PHARMACOLOGY OF CODEINE

Codeine exhibits little pharmacologic activity on its own. Analgesia and respiratory depression arise principally from

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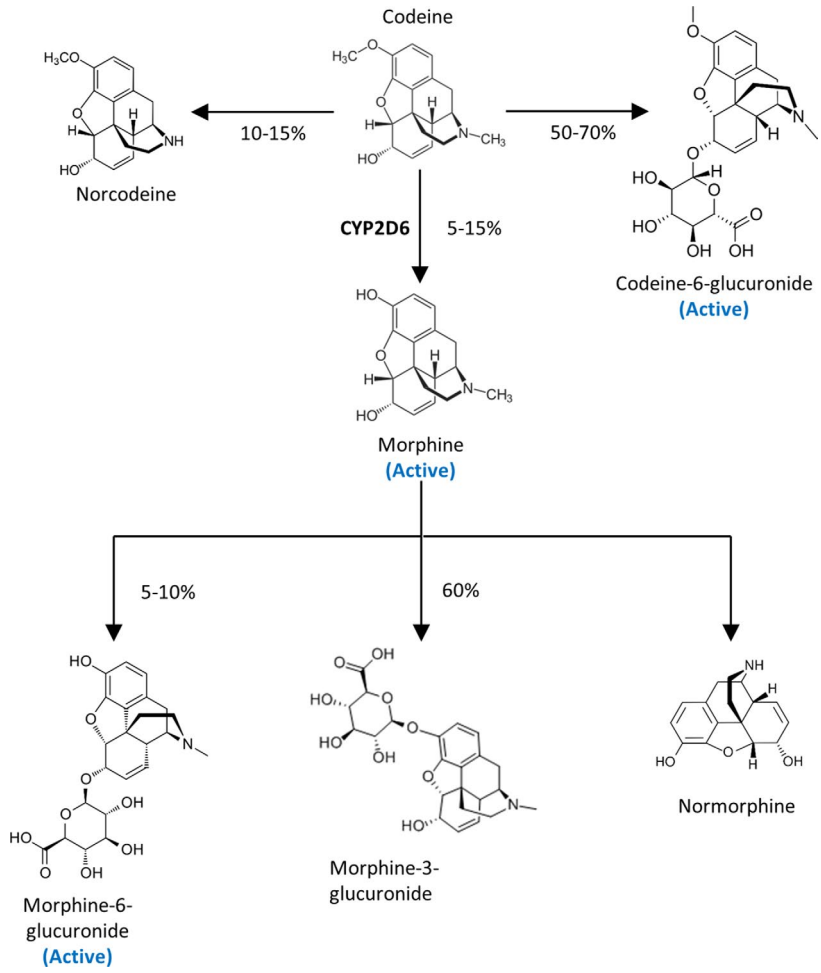

Figure 1 Codeine is converted by CYP2D6 to morphine, which is then metabolized to morphine-3-glucuronide, which is not an agonist at μ-opioid receptors, and morphine-6-glucuronide (M6G), a potent μ-opioid agonist. Although the pharmacokinetics of M6G in breastfeeding are not well-described, it confers considerably less respiratory suppression than morphine. Sedation and other opioid effects may also result from codeine-6-glucuronide. Percent values represent approximate metabolic contribution of each pathway.

its hepatic conversion to morphine by CYP2D6 (**Figure 1**).[8] Morphine is then metabolized to morphine-3-glucuronide and morphine-6-glucuronide (M6G), the latter of which imparts opioid effects.[8] Less widely appreciated is that sedation and other opioid effects may also result from codeine-6-glucuronide.[9,10]

The activity of CYP2D6, and hence the conversion of codeine to morphine, varies from person to person because of genetic polymorphisms, with the majority of white people (80–90%) displaying the "extensive metabolizer" (normal) phenotype.[11] Duplication of CYP2D6 genes is associated with increased enzymatic activity ("ultrarapid metabolizer" phenotype), whereas people with nonfunctional alleles exhibit a "poor metabolizer" phenotype, metabolizing codeine and other CYP2D6 substrate drugs poorly.[11]

The prevalence of CYP2D6 ultrarapid metabolizers is particularly high in North Africa and the Middle East, where up to a third of people exhibit the phenotype.[11] It is also found in up to 5% of white people.[11] In these individuals, conversion of codeine to morphine is modestly enhanced relative to extensive metabolizers, yielding, on average, 23% higher maximal morphine concentrations (C_{max}) and 45% higher total morphine exposure (**Table 1**).[12]

Table 1 Pharmacokinetics of codeine metabolism by genotype[12]

Phenotype	Peak codeine concentration, μg/L (median, range)	Peak morphine concentration, μg/L (median, range)	Codeine AUC μg·h/L	Morphine AUC μg·h/L
PM	45 (37–56)	0.05 (0.03–0.07)	180	0.5
EM	51 (24–104)	2.1 (0.6–4.3)	191	11
UM	43 (30–70)	2.6 (1.5–4.6)	192	16

Twenty-six patients (11 UM, 12 EM, and 3 PM) given a single dose of codeine 30 mg. The maximum concentration and total body exposure expressed as AUC of codeine and its metabolites were assessed over 24 hours after drug intake.
AUC, area under the concentration-time curve; EM, extensive metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.

OBSERVATIONS ON THE TORONTO CASE

Original interpretation

In the Toronto case, genotype analysis revealed the mother possessed a duplication of *CYP2D6*2*, consistent with an ultrarapid metabolizer phenotype. This observation, coupled with the finding of a high morphine concentration in breastmilk frozen 3 days before death (87 ng/mL), led investigators to conclude that the child died from opioid toxicity due to enhanced maternal conversion of codeine to morphine, with the subsequent passage of large amounts of morphine into breastmilk.[2,3] This interpretation of the case led the FDA and other major organizations to warn against the use of codeine by breastfeeding mothers.

Passage of opioids into breastmilk

The amount of drug ingested via breastfeeding is represented by the Relative Infant Dose (RID), an estimate of the average daily dose ingested by the infant, expressed as a percentage of the weight-adjusted maternal dose.[13] For example, an RID of 100% means that the infant receives the same daily dose per kilogram as the mother. The RID of most opioids ranges from 0.3% to 7.6% (**Table 2**).[13,14]

In the Toronto case, the neonatal postmortem blood morphine concentration of 70 ng/mL far exceeds that expected from breastfeeding alone. Breastfeeding neonates whose mothers take 60 mg of codeine every 4–6 hours for an average of 4 doses display morphine concentrations ranging from undetectable to 2.2 ng/mL.[15]

Not previously reported in the Toronto case was the postmortem neonatal codeine concentration of 300 μg/L obtained from the original toxicology report. This value is roughly 50 times higher than peak concentrations seen in neonates of mothers taking codeine while breastfeeding.[15] This obviously cannot be explained by maternal genotype, and suggests that conversion of codeine to morphine in the neonate (who was found to have an extensive metabolizer CYP2D6 genotype), rather than the mother, explains the elevated morphine concentration detected postmortem.

Table 2 Approximate relative infant dose of opioids[13]

Opioid	Primary metabolic pathway(s)	RID (%)[a]
Morphine	UGT2B7	2.5–7.5%
Codeine	CYP2D6	0.3–1.2%
Oxycodone	CYP3A4 (2D6, minor)	2.6–7.6%
Tramadol	CYP2D6	2.3%
Fentanyl	CYP3A4	1.2%
Hydromorphone	UGT	0.7%
Hydrocodone	CYP2D6/UGT	1.6–3.7%
Methadone	CYP3A4/2B6	1.2–7%
Buprenorphine	CYP3A4	0.4%

Enzymes responsible for opioid metabolism and estimated RID of opioids expected during breastfeeding.
CYP, cytochrome P450 enzymes; RID, relative infant dose; UGT, UDP-glucuronosyltransferase.
[a]Data from Lactmed: https://www.ncbi.nlm.nih.gov/books/NBK501922/, and e-lactancia: http://www.e-lactancia.org/.

Dose of morphine via breastmilk

An important inference can be drawn from the breastmilk morphine concentration noted above. At 87 ng/mL, had the baby ingested 1,000 mL of milk per day—roughly twice the amount expected for a baby of similar weight, and unlikely given the observation of poor feeding[2,3]—the resulting daily dose of morphine would be only 87 μg. In contrast, the suggested oral dose of morphine for a 4 kg infant is up to 3200 μg per day.[16]

The foregoing observations make clear that neither maternal CYP2D6 polymorphisms nor intake of codeine or morphine through breastmilk can, on their own, explain neonatal opioid toxicity, because the amount of opioid ingested is simply far too low.

Factors affecting the disposition of codeine and morphine in children

Other factors influence the metabolism and clearance of codeine and morphine in neonates. CYP2D6 activity begins to increase in the third trimester and then increases significantly within days to weeks of life.[17] Submaximal CYP2D6 activity in the first few weeks of life might impart reduced ability to convert codeine to morphine. In addition, morphine is converted to its active metabolite M6G by UDP-glucuronosyltransferase (UGT) 2B7. The child in the Toronto case was reported to be homozygous for UGT2B7 *2/*2,[3] which should lead to an increased ability to convert morphine to M6G. Like CYP2D6, UGT2B7 activity is low at birth; however, it increases with time into the early childhood years.[18,19] It is therefore difficult to quantify the impact of the UGT2B7 *2/*2 rapid metabolizer genotype. Importantly, although the activities of CYP2D6 and UGT2B7 could influence the disposition of codeine and morphine in the Toronto case, they cannot explain the extremely high neonatal codeine concentration.

Determinants of morphine accumulation

What circumstances might permit development of a toxic neonatal morphine concentration via breastfeeding during maternal codeine therapy? An elaborate pharmacokinetic modeling study by Willmann *et al*. has addressed this exact question.[7] The most important finding of this study was that neonatal morphine elimination, not the amount ingested, is the critical determinant of morphine accumulation. Irrespective of maternal codeine dose and CYP2D6 genotype, morphine concentrations exceeding 20 μg/L (20 ng/mL) are only predicted in neonates unable to eliminate morphine due to complete renal impairment.[7] Even a partially preserved ability to eliminate morphine would be sufficient to prevent neonatal toxicity. Complete absence of morphine excretion seems unlikely in the Toronto case, given the previously unreported observation that the child's pediatrician made note of five wet diapers on the day before death.

The pharmacokinetic "worst case scenario"

Willmann *et al*. modeled a pharmacokinetic "worst case scenario" by setting all pharmacokinetic parameters to their extremes, including a maternal codeine dose of 2.5 mg/kg/day and ultrarapid metabolizer status, efficient transfer of morphine into milk, and a complete absence of neonatal morphine clearance.[7] Under this

highly improbable set of conditions, the maximum achievable neonatal concentration of morphine after 14 days of normal milk intake was estimated at 54 μg/L, nearly 25% lower than observed in the Toronto case.[7] Of note, the maternal codeine dose employed in the Willmann simulation was lower than the actual dose, reflecting an error in the original report. Had the correct dose been used, a higher predicted neonatal morphine concentration would have resulted. Regardless, neonatal opioid toxicity would only be expected in the setting of negligible neonatal drug clearance. This point has also been emphasized by Ito in a recent review of the topic.[13]

Acetaminophen

An aspect of the Toronto case not originally reported was the postmortem acetaminophen concentration of 5.9 mg/L (39 μmol/L).[3] As Bateman and colleagues have observed, this concentration would be expected shortly after ingestion of a therapeutic dose of the drug.[6,20] Although acetaminophen passes freely into breastmilk, infants are expected to receive a maximum of only 5% of the maternal weight-adjusted dose through breastfeeding.[6]

Koren *et al*. have invoked postmortem changes in drug concentration to explain the acetaminophen finding.[21] Although there are little data regarding postmortem redistribution in neonates, several studies (indeed, including the one cited by Koren *et al*. in support of their claim[22]) demonstrate that acetaminophen exhibits little postmortem redistribution, particularly when samples are drawn within 24 hours of death, as was the case here.[23] Simply put, it is difficult to envision how a neonatal acetaminophen concentration of 5.9 mg/L could arise from breastfeeding alone.

Other reports of neonatal opioid toxicity from breastfeeding

We reviewed other published reports of suspected neonatal opioid toxicity from breastfeeding (**Table 3**). Most describe neonatal lethargy, apnea, or poor feeding that subsided after cessation of maternal opioid therapy. In most cases, data were obtained from retrospective interviews of parents regarding their children's behavior, sometimes years after the reported event. The informative value of these reports is undermined by the possibilities of self-selection and misclassification of exposures, outcomes, or both. In most reports, the association between maternal opioid use and adverse neonatal outcomes is questionable and not accompanied by pharmacokinetic data.

Some of these publications explicitly raised the possibility of neonatal opioid exposure via routes other than breastfeeding,[24,25] whereas others, upon closer inspection, are not consistent with opioid toxicity at all. The latter is best exemplified by a report of

Table 3 Other reports of suspected neonatal opioid toxicity from breastfeeding

Article	Details	Comment
Koren *et al*.[2] Madadi *et al*.[3]	Toronto case discussed herein	
Madadi *et al*.[29]	Neonate observed to be somnolent and breastfeeding poorly for the first 7 days of life, during which time the mother took codeine 120 mg per day. The mother reported drowsiness and was found to be a CYP2D6 UM. Cessation of breastfeeding was associated with resolution of neonatal symptoms.	Information collected from parental interview. No opioid concentrations reported.
West P *et al*.[30]	Mother who took two doses of methadone 40 mg. Her 13-month-old child developed an opioid toxidrome responsive to naloxone. The child's urine drug screen was positive for methadone.	No additional pharmacokinetic data. Methadone has an estimated RID of 3%. Authors acknowledge direct administration of methadone to the child as a potential explanation.
Levine *et al*.[24]	10-month-old child who died from a suspected oxycodone overdose. One day before death, the mother took oxycodone 60 mg and carisoprodol 700 mg, and on the day of death took hydrocodone 10 mg. The child had been febrile and the mother was administering acetaminophen. Postmortem liver and heart blood oxycodone concentrations were 1.6 mg/kg and 0.6 mg/L, respectively.	Mode of oxycodone exposure unclear but inconsistent with breastmilk as sole source. Carisoprodol (estimated RID 6%) not detected postmortem, as would have been expected. Coroner ruled death a homicide.
Meyer & Tobias[25]	5-week-old infant found cyanotic with minimal respiratory effort after a 4 to 5-day history of cough. The infant was intubated, admitted to the intensive care unit, and given naloxone i.v. with improvement in respiratory effort. The mother admitted to taking hydrocodone and methadone, and the child's urine drug screen was positive for opioids.	No accompanying pharmacokinetic data. Unclear how the child was exposed to a toxic dose of opioids.
Smith[26]	7-day-old breastfed infant with bradycardia and central nervous system depression 6 days after the mother took a single dose of codeine 30 mg.	Authors concluded symptoms were unlikely related to codeine given the dose and temporal relationship. No accompanying pharmacokinetic data.
Timm[31]	4-day-old infant presented to the ED with hypothermia, pinpoint pupils, and lethargy. The mother was breastfeeding and had taken 10 mg oxycodone the previous evening and 5 mg the morning of presentation to hospital. The child was given naloxone 0.34 mg i.v. resulting in awakening.	Maternal opioid dose was low and inconsistent with gradual accumulation of opioid in the neonate. Neonatal respiratory rate of 36 breaths/minute inconsistent with serious opioid toxicity. No accompanying pharmacokinetic data.

(Continued)

Table 3 (Continued)

Article	Details	Comment
Ito *et al.*[32]	Case series of children exposed to various drugs from breastfeeding. In 8 of 26 children whose mothers took codeine mothers reported neonatal drowsiness (5), irritability (1), and constipation (2).	Data collected by parental interviews at mean of 11.7 weeks after the initial call to the Motherisk Consult Service, raising possibilities of selection bias and misclassification of exposures, outcomes or both. No information on opioid dose or timing in relation to symptoms. No accompanying pharmacokinetic data.
Davis & Bhutani[33]	Case series of four infants (4–6 days old) with periods of apnea. Mothers were breastfeeding and receiving codeine 60 mg every 4–6 hours. Apneic episodes resolved after 24–48 hours following stopping codeine.	Alternative explanations for apnea not excluded. No pharmacokinetic data. Ages of children (4–6 days) is unlikely sufficient to allow significant neonatal morphine accumulation via breastfeeding.
Bodley & Powers[34]	Mother with mastitis who took hydrocodone 20 mg q4h while breastfeeding. Drowsiness in her and her 18-day-old child resolved after dose reduced to 20 mg daily.	Case focused on mother's health with only brief speculation of possible neonatal opioid toxicity. No pharmacokinetic data.
Lam *et al.*[27]	Case 1: Mother of healthy infant took oxycodone for 4 days then codeine for 3 days while breastfeeding. At 8 days, the baby had a respiratory arrest and received i.v. naloxone in the ED with clinical improvement. Morphine concentration in breastmilk was 30 ng/mL on the same day at the ED visit.	Child suffered from a presumed opioid toxidrome and responded to naloxone. No other pharmacokinetic data or information about maternal or neonatal drug clearance.
	Case 2: Lethargic 7-day-old infant was brought to hospital with pinpoint pupils and received i.v. naloxone with clinical improvement. The mother had been taking codeine and was breastfeeding the child.	Personal communication between the authors and a colleague. No information presented about maternal codeine dose. No accompanying pharmacokinetic data.
	Case 3: A 3-day-old infant was lethargic and difficult to rouse. The mother had been taking codeine 240 mg/day while breastfeeding. The symptoms subsided when codeine was stopped. The mother was found to be a CYP2D6 extensive metabolizer.	Anecdote of nonspecific neonatal signs improving after cessation of maternal codeine. No accompanying pharmacokinetic data.
	Case 4: A 2-day-old infant too sedated to expectorate mucus experienced had a respiratory arrest. The mother was taking codeine at an unknown dose. The infant's urine was positive for morphine, and symptoms improved upon cessation of breastfeeding.	Cases 4–6 obtained from Health Canada online reporting system. Entries into this database can be made by anyone. Data are limited and of unknown validity.
	Case 5: A 4-day-old infant was drowsy and difficult to rouse. The mother was taking codeine at an unknown dose. Symptoms improved after cessation of breastfeeding.	
	Case 6: A 7-day-old breastfeeding infant was lethargic and difficult to rouse. The mother was taking codeine up to 6 times a day at an unknown dose. The child's symptoms improved over the course of a hospitalization.	
Naumburg & Meny[35]	Case-control study involving 12 infants (12 hours to 7 days old) with unexplained apnea, bradycardia, or cyanosis matched to 16 asymptomatic infants. The mothers of 10 of 12 case infants took opioids (codeine, propoxyphene, meperidine) while breastfeeding, compared with 11 of 16 with little or no opioid exposure.	Pharmacokinetic data available only for one case. The infant had a serum morphine level of 1.2 ng/mL 108 hours after the mother's last dose of morphine. No morphine detected in breastmilk at that time.
Madadi *et al.*[29]	Case-control study of symptomatic infants whose mothers took codeine (n = 17) matched to asymptomatic infants whose mothers took codeine (n = 55). Cases had 59% higher daily doses of codeine (1.62 ± 0.79 mg/kg/day vs. 1.02 ± 0.54 mg/kg/day (P = 0.004)).	Data primarily acquired by interview. CNS depression defined by parental report of sedation or abnormal breathing in the infant during the period of codeine use while breastfeeding. Previously reported cases (Koren[2]; Madadi[3]; and Madadi 2009 described in detail above) were included as cases. No supporting pharmacokinetic data beyond the case described herein.
Lam *et al.*[36]	Retrospective case series comparing the risk of CNS depression in neonates of mothers who took oxycodone, codeine (± acetaminophen), or acetaminophen only while breastfeeding. In the oxycodone cohort, (n = 139) 20.1% of mothers reported neonatal "CNS depression" compared with 16.7% in the codeine group (n = 210), and 0.5% in the acetaminophen group (n = 184). The rate of CNS depression in infants of mothers receiving codeine did not meet the predefined threshold for statistical significance. Higher doses of oxycodone and codeine were associated with increased reported neonatal symptoms.	High risk of selection and recall biases. All mothers voluntarily called the Motherisk Program to be included in the study. They were contacted in follow-up sometimes years after the original call to Motherisk and were asked about infant symptoms. Some of the subjects in the codeine cohort were from Madadi[29].

CNS, central nervous system; ED, Emergency Department; RID, Relative Infant Dose; UM, ultrarapid metabolizer.

neonatal bradycardia and central nervous system depression occurring 6 days after maternal use of a single 30 mg codeine tablet.[26] Although a causal relationship is clearly implausible in this case, it has nevertheless been cited as an instance of neonatal opioid toxicity resulting from maternal use of codeine while breastfeeding.[27]

Only one other publication describes neonatal death in the setting of maternal opioid use while breastfeeding. In that report, a 10-month-old child died of suspected oxycodone toxicity, although the child was also found to have multiple head injuries.[24] The authors of the report were openly skeptical about the possibility of breastmilk as the sole source of oxycodone.

We are aware of no other published reports of neonatal death due to opioids passed through breastmilk, despite millions of postpartum women having taken opioids over the past 2 decades. This observation is consistent with the findings of a cohort study of 7,804 new mothers prescribed codeine within 7 days of discharge, which found no evidence of neonatal harm on several measures, including all-cause hospitalization, injury, resuscitation/mechanical ventilation, or death from any cause.[28]

CONCLUSIONS

Neonatal opioid toxicity resulting from maternal codeine use during breastfeeding could only arise from a highly improbable combination of factors: a high maternal codeine dose, unusually high concentrations of opioids in breastmilk, a large volume of neonatal milk intake, and—critically—profoundly impaired neonatal opioid clearance. The unlikely occurrence of such a scenario is consistent with the paucity of reports of neonatal opioid toxicity, despite the use of these drugs by millions of nursing mothers over the past 2 decades.

This should not be viewed as an endorsement of opioid use while breastfeeding. Codeine, in particular, is an unpredictable analgesic choice given its variable conversion to morphine, whereas other opioids, such as oxycodone, carry greater abuse liability. Acetaminophen and nonsteroidal anti-inflammatory drugs are generally sufficient for the management of postpartum pain. When opioids are required, short courses should not be viewed as hazardous to breastfeeding neonates.

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CONFLICT OF INTEREST

D.J. is an unpaid member of Physicians for Responsible Opioid Prescribing (PROP), which is sometimes cast as an "anti-opioid" group but in actuality is invested in safer and more evidence-based opioid prescribing. D.J. is also a member of the American College of Medical Toxicology. Both PROP and ACMT have publicly available positions related to opioid prescribing. D.J. has received payment for lectures and medicolegal opinions regarding the safety and effectiveness of analgesics, including opioids; J.Z. has no conflicts of interest to declare.

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