PERSPECTIVE

Opioid Use in Breastfeeding Mothers and Neonatal Risks

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Historically, clinicians opted for discontinuing breastfeeding while mothers consumed almost any medication. Now the presumption is, "how can we keep mothers breastfeeding despite medications?" Simultaneously, the use and abuse of opioid medications have swept through the breastfeeding population. Is the benefit of breastfeeding higher than the risk of exposure to opioids? If so, how can we manage this difficult conundrum? This perspective provides insight on management of opioids in breastfeeding mothers while safeguarding the infant.

Factors that affect transfer of drugs such as opioids into human milk

The ability of a drug to transfer into the milk compartment is enigmatic but largely a function of its physiochemistry (see **Table 1**). Drugs with low molecular weight, low protein binding, and high pKa tend to transfer at higher levels. Opioids generally fit these parameters and transfer to some degree into human milk. Ultimately, the level of transfer of all medications into milk is dependent on the dose. This is a major risk factor in the use of opioids, as many chronic opioid users use extraordinarily high doses. The relative infant dose (RID) is calculated as a weight-adjusted percentage of maternal dose. Although RIDs have only been established for ~ 300 currently available medications, opioids are strongly represented. Unfortunately, the RID does not include all factors needed for a risk-benefit evaluation, particularly the infant's tolerance.

Stage of lactation and its effect on risk

The stage of lactation plays a major role in the dose of drug transferred to the infant. If exposure occurs in the early postnatal period (colostrol period), the total daily volume of milk produced by the mother is rather minimal (60–100 mL), therefore, the dose to the infant is likely minimal. However, after 2–4 weeks postpartum, the production of milk increases dramatically, sometimes up to 600–700 mL per day. Exposure of infants to maternal drugs at this point needs careful consideration, as the dose delivered to the infant can be quite high. As the infant nears 10–12 months of age, the intake of maternal milk is reduced, and their metabolic capacity is roughly equivalent to an adult posing less risk of drug accumulation. After 12–18 months postpartum, the total milk ingested by the infant drops significantly (20–100 mL/day). Infants exposed in "late stage lactation" are subject to reduced risk.

Opioids all pose a potential risk of sedation and apnea. Although we can estimate the transfer of drug into milk, estimating the response in infants is difficult. For decades, hydrocodone, oxycodone, and codeine have been widely used for managing postpartum pain in millions of mothers. In 2017, the US Food and Drug Administration (FDA), American College of Obstetricians and Gynecologists (ACOG), and the Academy of Breastfeeding Medicine advised that codeine and tramadol should be withheld or restricted in breastfeeding mothers and children due to potential effects of ultrarapid CYP2D6 metabolism to morphine.[1] However, they did not make any suggestions for safer alternatives. A balance must be found between an opioid and its perceived risk of neonatal toxicity.

Morphine. Morphine is the standard opioid by which all other analgesics are compared in breastfeeding mothers. Ten percent of morphine is metabolized to morphine-6-glucuronide.[2] Although M6G is more potent than morphine with less protein binding and higher levels in human milk, its penetration of the blood-brain barrier is slow.[3] M6G has an elimination half-life similar to morphine, ranging from 2.9–4.5 hours and has been found in milk. Doses as high as 15 mg i.v./i.m. have produced relative infant doses as high as 35% and milk levels of 50 μg/100 mL. Fortunately, the oral bioavailability of morphine in adults, and presumably infants, is < 30%, thus reducing exposure in the infant as well.[3]

The clearance of morphine in infants begins to approach adult values by 2 months of age. High doses over prolonged periods can lead to accumulation, sedation, and respiratory problems in newborn infants, so maternal doses should be low. Studies of

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Table 1 Common properties of opioid analgesics

	MW, daltons	Protein binding	Oral bio	$T_{1/2}$, hours	RID	DEA schedule	MME
Buprenorphine	504	96%	29%	2–3	< 1–3%	III[a]	10
Codeine	299	7%	53%	2.9	< 1–8%	III[b]	0.15
Hydrocodone	299	19–45%	25%	3.8	2–4%	II	1
Hydromorphone	321	8–19%	60%	2.6	1%	II	4
Methadone	309	89%	50%	13–55	2–7%	II[a]	4-12[c]
Morphine	285	35%	26%	2	2–7%	II	1
Oxycodone	351	45%	60–87%	2–4	1–5%	II	1.5
Oxymorphone	337	12%	10%	7.8	unk	II	3
Tramadol	263	20%	60%	7	3%	IV	0.1

DEA, Drug Enforcement Administration; MME, Morphine Miligram Equivalents; MW, Molecular Weight; RID, relative infant dose; $T_{1/2}$, terminal half-time; unk, unknown.
[a]Additional DEA requirements for prescribing. [b]For substances < or = to 90 mg per dosage unit. [c]Dose dependent.

the neurobehavioral outcome in breastfed infants suggest morphine is a good choice, providing excellent maternal pain relief with minimal impact on the infant.

Codeine. Codeine is a prodrug, with minimal activity at the opiate receptor. Eighty percent of codeine is inactivated by metabolism to codeine-6-glycoronide and norcodeine. Only 0–10% of codeine generally undergoes demethylation to morphine by CYP2D6, an enzyme with known genetic polymorphisms.[2] The incidence of poor metabolizers ranges from 2–10% based on ethnicity. Ultrarapid metabolizers may represent 1–30% of the population, and result in higher concentrations of morphine in the plasma in the short term. Further, an infant's susceptibility to adverse events is higher during the neonatal period (first or second week) as their hepatic metabolism and renal clearance is quite poor.[4]

The use of codeine in breastfeeding mothers is still controversial. The hallmark publication of a 2005 neonatal opioid toxicity resulting in the death of an infant in Toronto[5] has always been somewhat controversial with those of us in breastfeeding pharmacology. The infant levels of both drugs in this publication exceeded the reality of published comparisons. The presence of these extraordinarily high levels of morphine, and particularly acetaminophen, is highly questionable from breastmilk as a source. The etiology of this poisoning has always been in question. Did the levels arise from maternal rapid metabolism and infant accumulation, or from some other external source? A recent article by Zipursky and Juurlink make a strong argument against breastmilk as the sole source of this overdose.[6]

Without doubt, millions of breastfeeding mothers have used codeine over the last 50 years. Interestingly, the use of codeine is now rebounding with the restrictions placed on hydrocodone, which was the most prevalent opioid used as little as 6 years ago. As a case of unintended consequences, the number of acetaminophen/codeine 300/30 mg and 300/60 mg combination products increased by 597% and 1,056%, respectively, in the months after combination hydrocodone products were reclassified as DEA Schedule CII. During the same time period, the number of hydrocodone/acetaminophen 5/325 mg prescriptions decreased by 58%.[7]

In the vast majority of mothers, codeine consumed in moderation and for a short duration is probably suitable for their breastfed infant. However, due to an abundance of caution by some agencies, this product is not generally recommended for use by breastfeeding women, although its use is widespread. Ultimately, the infant's response to exposure to codeine in milk should be monitored closely. Any report of somnolence, apnea, poor feeding, or signs of cyanosis could be associated with exposure to codeine in breast milk.

Hydrocodone. Hydrocodone is 30-fold less bioactive than its active metabolite hydromorphone.[2] Levels of these drugs were measured in 30 women who were receiving 10–15 mg/day of hydrocodone for postpartum pain.[8] These fully breastfed infants received on an average 2.4% of the maternal hydrocodone dose. The total dosage to infants was estimated at 0.7% of their neonatal therapeutic dose, suggesting that standard maternal doses are clinically irrelevant to the infant.

Hydrocodone is still generally recommended for treatment of postpartum pain, and doses should be limited to 30 mg/day. If higher doses are required, then the infant should be closely monitored for possible untoward complications, such as sedation and apnea. Doses more than 40 mg/day should be avoided.[8]

Oxycodone. The analgesic effect of oxycodone is primarily due to the parent drug itself.[2] Compared with morphine, both parent and metabolite are more potent but exhibit a reduced adverse profile. Oxycodone has a milk/plasma ratio of up to 3.4 and has been detected in milk for up to 37 hours in 10% of participants. These plasma and milk levels suggest that oxycodone may concentrate in the milk compartment. However, detectable levels of oxycodone in the infant's plasma are rare.[9]

There are at least two case reports suggesting a dose-related risk of infant sedation following maternal ingestion of oxycodone. The use of doses > 40 mg/day are discouraged in opioid-naive breastfeeding mothers. Higher doses may be acceptable in breastfeeding mothers who received opioids regularly during their pregnancy.

Methadone. Methadone is a potent and very long-acting opioid analgesic structurally unrelated to morphine. It is primarily used

to prevent withdrawal in opioid addiction. Methadone has a high affinity for the mu receptor and is difficult to displace from the receptor, hence its usefulness in treating heroin abuse.[2]

More than 65 patients have been studied with methadone while breastfeeding an infant. Relative infant doses in breastfed infants range from 1.9–6.5% of moderate maternal doses. In general, methadone can be safely used in breastfeeding mothers as long as the dose does not exceed 180 mg. Mothers consuming doses above 180 mg/day should be advised not to breastfeed.

Liberal methadone use during pregnancy and breastfeeding will probably predispose the infant to some degree of dependence. Mothers should be advised to withdraw themselves and their infants carefully should they want to discontinue breastfeeding. Following birth, the amount of methadone in milk is insufficient to prevent neonatal opioid withdrawal, but may be enough to suppress serious withdrawal in the infant. Usually, infants will require some exogenous morphine or methadone to prevent withdrawal.

Buprenorphine. Buprenorphine is another potent and long-acting semisynthetic opioid with a unique dual mechanism of agonism/antagonism.[2] The pharmacokinetics of this drug vary widely with its different formulations, which may necessitate further evaluation.

Buprenorphine is used frequently and successfully in breastfeeding mothers, likely due to its low RID (< 0.1–2.5%) and poor oral bioavailability. However, studies characterizing the RID frequently only evaluate usual doses between 2 and 22 mg. A higher mother's dose and/or an infant with suspected lower tolerance to opioids may prompt consideration for more conservative care.

DISCUSSION

All opioids will transfer into human milk to some degree. Maternal doses should always be considered for safety in breastfeeding women. We have extensive experience with morphine, hydrocodone, and codeine over the last 40 years. Morphine, when used judiciously and in low to moderate doses, is apparently safe to use. Codeine has without doubt been used in millions of mothers over that last half century worldwide with minimal problems reported. One death associated with codeine in the United States has led to advisories discouraging its use in breastfeeding women. However, recent reviews have successfully documented the implausibility of this case report.[6] Hydrocodone has been the primary opioid used postnatally in the United States for decades, with good outcomes.

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CONFLICT OF INTEREST

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