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Hydrocodone Excretion into Breast Milk: The First Two Reported Cases

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ABSTRACT

Hydrocodone is a narcotic that is widely used, often in nursing mothers. Although case reports suggest that hydrocodone in breast milk sometimes may be problematic for the breastfed infant, no reports exist on the amount of its excretion into breast milk. Two mothers who were taking an acetaminophen and hydrocodone combination product donated pumped milk for analysis of hydrocodone. Their infants received an estimated 3.1% and 3.7% of the maternal weight–adjusted dosage, but the absolute hydrocodone dosages were 8.58 μg/kg per day and 3.07 μg/kg per day because of the differences in the dosages ingested by their mothers. Moderate dosages of hydrocodone appear acceptable during breastfeeding, but more data are needed to determine the maximum safe dosage for nursing mothers. Neonates and preterm infants may be more susceptible than older infants to adverse effects of hydrocodone and its metabolites in breast milk.

INTRODUCTION

THE COMBINATION PRODUCT hydrocodone and acetaminophen (Vicodin, various) was ranked as the most dispensed generic pharmaceutical in community pharmacies in the United States in 2005, with nearly 102,000,000 prescriptions dispensed.[1] This product is often used in postpartum mothers, especially following Cesarean section. However, information on the excretion of hydrocodone into breast milk is lacking. Two published cases indicate that there may be cause for concern about hydrocodone in breast milk during the newborn period.

The 18-day-old infant of a breastfeeding mother became groggy and "slept for most of the day," while the mother was taking 20 mg of oral hydrocodone combined with 1300 mg of acetaminophen every 4 hours for painful nipple candidiasis and mastitis. The mother decreased her dose by one-half and the infant apparently no longer experienced grogginess or hypersomnolence.[2]

A 5-week-old breastfed infant became cyanotic and required mouth-to-mouth resuscitation and intubation. The infant's urine was positive for opioids and the infant responded positively to naloxone; the level of consciousness improved over 2 days and extubation was

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accomplished. The infant's mother admitted to taking a hydrocodone-acetaminophen combination product and methadone that had been prescribed for migraine headache before she was breastfeeding.[3]

These case reports were rated using the Naranjo algorithm,[4] which is a method for determining the likelihood that an adverse reaction was caused by a drug. Both were rated as "probable" by this method, although the relative contributions of hydrocodone and methadone to the adverse reaction in the second case cannot be determined.

MATERIALS AND METHODS

The authors studied the breast milk of two mothers who were nursing their newborns and taking tablets containing hydrocodone 5 mg and acetaminophen 500 mg during their hospitalization. Both women consented to having aliquots of their pumped breast milk analyzed for hydrocodone in accordance with UCSD IRB guidelines.

Case 1

Patient 1 is a 22-year-old, 63.6-kg primiparous woman who had been prescribed hydrocodone plus acetaminophen during the third trimester of her pregnancy for headache associated with a newly diagnosed left-sided temporal schwannoma (skull base tumor). She delivered her baby at 35 + 0 weeks gestation by elective Cesarean section. During her postdelivery hospitalization, the mother required one to two tablets of the hydrocodone combination three to four times a day to control her headache. The mother and baby's immediate postpartum period was otherwise uneventful and both were discharged home on postpartum day 4. On postpartum day 7 the mother was readmitted for a scheduled left temporofrontal craniotomy with excision of her tumor. In the immediate (90-minute) postoperative period she received a total of 8 mg of intravenous hydromorphone for pain in the postanesthesia care unit. Upon transfer to the surgical intensive care unit, hydromorphone was discontinued and she then began taking the hydrocodone combination one to two tablets orally every 4 hours as needed for pain. This regimen was continued throughout her 5-day postoperative hospital stay. During this time, the patient pumped her breasts with a hospital-issued electric breast pump at 3- to 5-hour intervals. At each pumping, both breasts were emptied and milk was collected in 5-fluid-ounce plastic bottles.

With her consent, the authors obtained samples (>10 mL) of the patient's collected milk for the purpose of measuring hydrocodone concentrations. The first study milk samples were initially stored at room temperature shortly after collection by the patient's nurse on the nursing unit for 4 to 8 hours prior to transfer to the pharmacy, where it was stored at −20°C until transfer to the laboratory for assay. The patient's hydrocodone use and breast milk concentrations are shown in Table 1. Other medications taken during the milk collection period

Table 1. Patient 1 History

Date	*Time*	*Hydrocodone bitartrate dose (mg)*	*Milk hydrocodone (μg/L)*
2/16	5:00	10	
	10:00	10	
	14:00	10	
	22:45		48.1
2/17	4:10	10	
	4:30		8.6
	9:30		33.1
	12:10	10	
	14:00		59.7
	18:10		61.0
	18:40	10	
	22:30		62.7
	22:40	5	
	22:45		21.3
2/18	2:15		127.3
	6:30		97.0
	6:40	5	
	10:40	5	
	14:45		67.9
	15:35	5	
	16:50		70.0
	19:15		56.5
	19:47	5	
	21:29	5	
	22:30		98.1
2/19	5:00	5	
	6:40	5	
	9:15		53.6
	13:50	5	
	14:15		29.1
	19:30		26.4

included acetaminophen 650 mg as needed (1 dose/day received), cefazolin 1 g every 8 hours for three doses through postoperative day 1, famotidine 20 mg IV every 12 hours, and docusate 100 mg orally three times daily.

Case 2

Patient 2 is a 22-year-old, 73.5-kg woman who delivered her second infant by Cesarean section. On day 16 postpartum, she presented to the emergency department with chief complaints of fever, body aches, burning on urination, chills, and sweats. She also had a painful 3-cm area of erythema around her left nipple, which was diagnosed as mastitis. Her surgical site was noted to be healing well, but she was hypotensive with a blood pressure 82/41 mmHg, tachycardic at 130 beats/minute and had an abnormal urinalysis with elevated white blood cell count and a few bacteria. She was initially treated with 2 L of 0.9% sodium chloride intravenously in the emergency department and then admitted with a diagnosis of urosepsis. Her inpatient medications included vancomycin 750 mg IV every 8 hours, ceftriaxone 1000 mg IV once daily, heparin 5000 units subcutaneously every 8 hours, docusate 250 mg orally once daily, and 5 mg hydrocodone plus acetaminophen 500 mg every 6 hours as needed for pain. She pumped her breasts with an electric breast pump during her hospitalization. The pumping was to collect milk to feed her infant who was at home, and to help with her mastitis. With her consent, the authors obtained samples (>10 mL) of the patient's collected milk for the purpose of measuring hydrocodone concentrations. Milk samples were frozen at −20°C until analyzed. The patient's hydrocodone use and breast milk concentrations are shown in Table 2.

Table 2. Patient 2 History

Date	*Time*	*Hydrocodone bitartrate dose (mg)*	*Milk hydrocodone (μg/L)*
3/23	21:40	5	
3/24	5:10	5	
	15:15		16.6
	18:15		9.4
	21:30		5.2
	22:30	5	
3/25	2:10		47.2
	9:00		26.1

Hydrocodone assay

Aliquots of breast milk pumped by the mothers were analyzed for hydrocodone by ELISA assay (OraSure Technologies, Bethlehem, PA). The assay was modified to enhance quantitative accuracy. With the modifications, the limit of quantitation was 0.1 μg/L. For assay validation, naïve breast milk samples were spiked with hydrocodone; the results are shown in Table 3. Breast milk samples spiked with hydrocodone were also stored overnight at room temperature and found to yield accurate results.

Pharmacokinetic analysis

To calculate the total dose of hydrocodone received by the infants of these two mothers, the area under the milk concentration–time curve (AUC_{0-t}) was estimated using a linear rectangular method described previously.[5] The average milk concentration over the study period was then calculated by dividing the AUC by the number of hours in the sampling period. This value was then multiplied by the accepted average milk intake value of 150 mL/kg per day to estimate the infant dosage in μg/kg per day.

The total dosage that each mother ingested was divided by the total number of hours that the mother was studied and multiplied by 24 to calculate an average daily dosage. This dosage was then divided by maternal weight to calculate the average maternal hydrocodone dosage in μg/kg per day. Because hydrocodone USP is the bitartrate hemipentahydrate (2.5 waters of hydration), the authors multiplied the dosage that the mother received by a factor of 0.605 to determine the dose of anhydrous hydrocodone base that she ingested.

Finally, the infant's estimated dosage in μg/kg per day was divided by the average maternal dosage in μg/kg per day. This value was multiplied by 100 to calculate the weight–adjusted percentage of maternal dosage that the infant received.

Table 3. Hydrocodone Assay Validation

Amount added to milk (μg/L)	*Assayed value (μg/L)**
0	0
0.5	0.4
5	5.4
50	47.9

*Sample values above 100 μg/L were extrapolated.

RESULTS

Patient 1 received a total of 63,525 μg (998.8 μg/kg) of hydrocodone base during the 86.5 hours of milk collection (see Table 1). The AUC of the drug concentration in milk during this time was 4946.1 μg/L · hr, yielding an average milk concentration of 57.2 μg/L. If exclusively breast milk fed, her infant would receive a dose of 8.58 μg/kg per day, or 3.1% of the maternal weight–adjusted dosage.

Patient 2 received a total of 9075 μg (123.5 μg/kg) of hydrocodone base during the 36-hour period of milk collection (Table 2). The AUC of the drug concentration in milk during this time was 735.6 μg/L · hr, yielding an average milk concentration of 20.4 μg/L. Her infant would receive a dose of 3.07 μg/kg per day, or 3.7% of the maternal weight–adjusted dosage.

Because the infants were not hospitalized with their mothers, the authors were unable to determine if either infant experienced an adverse reaction to the hydrocodone in breast milk.

DISCUSSION

This paper reports the first measurements of the widely used oral narcotic hydrocodone in breast milk from two hospitalized mothers who were pumping their breasts to provide milk for their nonhospitalized infants. The infants received less than 10% of the maternal weight–adjusted dosage, which is considered to be an acceptable limit for a medication in milk. However, even though the percent of maternal weight–adjusted dosage was slightly lower for infant 1 than infant 2, infant 1 received almost three times the absolute dose of hydrocodone as infant 2 because patient 1 took a much higher dosage of hydrocodone than patient 2 during the study period. The notion of 10% of the maternal weight–adjusted dosage being acceptable may not necessarily indicate absolute safety for the breastfed infant when a drug has a very wide maternal dosage range.

Additionally, the authors' methodology likely underestimated the total impact of maternal hydrocodone ingestion on the infant because it did not account for the active metabolites of hydrocodone. A major active metabolite is hydromorphone, which is a somewhat more potent narcotic than hydrocodone itself. This metabolic conversion is carried out by CYP2D6, which is under genetic influence, with extensive metabolizers having about five times the peak blood concentrations of hydromorphone as poor metabolizers.[6] In extensive metabolizers, average blood concentrations of hydromorphone are about 24% of hydrocodone concentrations, whereas in poor metabolizers, average blood levels of hydromorphone are only about 4% of hydrocodone concentrations.[6] A recent case report of fatal poisoning of an infant by high concentrations of morphine in the breast milk of a nursing mother who was a CYP2D6 supermetabolizer receiving oral codeine illustrates the importance that genetics can play in determining the safety of medications given to nursing mothers.[7]

If a 60-kg mother were to receive the maximum recommended dosage of 10 mg of hydrocodone bitartrate every 4 hours around the clock (1 mg/kg per day), an exclusively breastfed infant would receive an average of 3.4% of this dose, or 34 μg/kg per day based on the results in these two patients. A dosage of 600 μg/kg per day has been suggested for hydrocodone bitartrate in children under 2 years of age.[8] Although the dosage in milk is well under this value, it is likely that the dosage requirements for newborn infants are much less than that of a 2-year-old child. In fact, age appears to be a critical factor in determining susceptibility to adverse reactions from drugs in breast milk. An extensive review of the published literature on adverse reactions from maternal medications in breastfed infants found

that 78% of published cases occurred in infants under 2 months of age and only 4% of published cases were in infants over 6 months of age.[9] Infants reported to have adverse reactions involving hydrocodone were 18 days and 5 weeks of age.[2,3] Similarly, the death from codeine and its metabolites in breast milk occurred in a 13-day-old infant.[7]

Although many thousands of prescriptions for oral opiates are given annually to nursing mothers in the early postpartum period, there are no well-controlled studies on the incidence, severity, or dose–response relationship of adverse reactions in the breastfed infants of these mothers. This important area is in need of further study.

CONCLUSION

Low doses of oral hydrocodone appear to be acceptable for use in nursing mothers, but high doses in mothers who are nursing newborn or preterm infants, or in rare mothers who are CYP2D6 supermetabolizers may be of concern. Instructing mothers to watch for excessive sedation in their infants and monitoring infants for adequate weight gain during maternal hydrocodone use are reasonable precautions. Further studies on this widely used narcotic during breastfeeding are warranted.

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