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## CASE REPORT

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# Oxycodone Intoxication in an Infant: Accidental or Intentional Exposure?

**ABSTRACT:** A case is presented of a 10 month old male who went into cardiac arrest at a local store. The infant subsequently expired and was autopsied at the Office of the Chief Medical Examiner, State of Maryland. The only remarkable finding was the detection of oxycodone in the postmortem specimens; the blood and liver oxycodone concentrations were 0.6 mg/L and 1.6 mg/kg, respectively. Oxycodone was identified and quantitated by gas chromatography-nitrogen-phosphorus detection and confirmed by full scan electron ionization gas chromatography-mass spectrometry. The medical examiner ruled that the cause of death was oxycodone intoxication, and the manner of death was homicide. The key toxicologic question in this case was whether or not it was reasonable for the infant to be exposed to oxycodone exclusively through breast milk or through an alternate source. It was concluded that, at best, there were serious concerns about the likelihood of drug exposure through consumption of breast milk.

**KEYWORDS:** forensic sciences, oxycodone, postmortem, breast milk, infant

Oxycodone is a semisynthetic opioid agonist derived from thebaine. It has been used in combination with salicylate and acetaminophen as an analgesic with good bioavailability (1). Recently, a sustained release form of oxycodone has been developed for patients with chronic pain. The use of oxycodone is not recommended for children (2).

The increased use of oxycodone has led to an increase in its abuse. This abuse has occurred as an untoward effect of its therapeutic use or through its diversion from legitimate use to illicit use. Over the past five years, the detection of oxycodone in cases investigated by the Office of the Chief Medical Examiner, State of Maryland has increased significantly. In 1998, oxycodone was detected in 27 cases; this increased to 99 cases in 2003.

The following is a report of a case investigated by the Office of the Chief Medical Examiner of the death of an infant from oxycodone intoxication.

### Case History

The decedent was a 10-month old, African American male. At approximately 2100 hours, police officers responded to a call of a cardiac arrest at a local toy store. Upon their arrival, paramedics were administering cardio-pulmonary resuscitation (CPR) to the infant who was subsequently transported to the hospital where he was pronounced deceased at 2233 hours. Investigation revealed that the mother and her infant son arrived on a flight to Baltimore at approximately 0900 hours that morning. The grandmother, with whom the mother of the decedent and two other siblings was staying, stated that the infant had "not been fully awake since that morning." His medical history was significant only for a recent 102°F fever, which the mother was allegedly treating with acetaminophen.

The mother of the decedent had a significant medical history of "anxiety, auto immune disease, cluster headaches, depression, chronic intractable pain syndrome, migraine, muscular dystrophy, and lumbar radiculoneuropathy/muscle spasm." She was currently prescribed Roxycodone® (30 mg PO qid), Fiorcet® with codeine #3 (1 tablet PO qid), and Soma® (350 mg PO qid). She had prescriptions from previous doctors for multiple other medications including alprazolam, hydrocodone, amitriptyline, mirtazapine, venlafaxine, and neurontin. Both the mother and her husband had been instructed that she was not to breast-feed while taking these medications. In fact, the husband had called child protective services earlier in the year to report his wife was "... abusing her medications while the children are in her care ..." with specific concerns about her breast-feeding.

On the day prior to her son's death, the mother admitted to taking two 30 mg oxycodone tablets (Roxycodone®) at 1100, 1430, and 1700 hours and two 350 mg carisoprodol tablets (Soma®) at 1100, 1430, 1700, and 2000 hours. However, on the day of his death, she stated she only took one hydrocodone tablet (Lorcet®) at 0700 and 1430 hours. She further claims that she had been breast-feeding the baby only three times daily since earlier that year, as she was adding solid food to the baby's diet; on the day of his death, she claims he was breast-fed once on the plane (~0700 hours) and once again at ~1000 hours after his meal of cereal, juice, and fruit at ~0930 hours. In various interviews with the grandmother and the mother, the baby is noted as having been "drowsy" and "asleep" for the rest of the day and evening after the 1000 h feeding. Additionally, the grandmother stated that, as they were leaving to go

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shopping at the toy store (~1930 hours), the baby was breathing "funny" and "snoring" and further stated it sounded like he was congested and "having trouble breathing."

The autopsy was significant only for focal contusions of the forehead and chin with focal subgaleal hemorrhage of the right posterior parietal scalp. Microscopically, there was evidence of congestion and edema of the lungs with focal intra-alveolar hemorrhage and occasional intra-alveolar macrophages. Routine specimens were submitted for toxicologic analysis.

## Materials and Methods

*Oxycodone Analysis*

Oxycodone extraction was performed as follows: to 5 mL calibrator, blood, or tissue specimen were added 2 mL 0.1 N sodium hydroxide, 100 uL 100 mg/L ethylmorphine (internal standard solution), and 21 mL n-butyl chloride. After mechanical rotation and centrifugation, the n-butyl chloride layer was separated and extracted with 3 mL 1 N sulfuric acid. The acid layer was removed, alkalinized with 0.5 mL ammonium hydroxide, and extracted with 5 mL methylene chloride. The methylene chloride was transferred to a conical centrifuge tube, and 200 uL isopropanol was added. The methylene chloride was evaporated to the isopropanol layer at 40°C and was then transferred to an autosampler vial for GC analysis.

Quantitation was based on the area ratio of oxycodone to internal standard of the case specimen in comparison to a 1.0 mg/L calibrator. Two blood controls at concentrations of 0.2 and 1.0 mg/L also were analyzed in the batch. The limit of quantitation of the assay was 0.1 mg/L, and the upper limit of linearity was 6.0 mg/L.

Analysis was performed on a Hewlett-Packard (Palo Alto, CA) 5890 gas chromatograph (GC) equipped with a nitrogen-phosphorus detector (NPD). The column was a J&W Scientific (Folsom, CA) DB-5MS 5% phenyl-methyl-silicone fused capillary column (20 m × 0.18 mm I.D. × 0.18 μm film thickness). Helium was the carrier gas flowing at 1 mL/min. The injector temperature was 260°C with a detector temperature of 280°C. The oven temperature began at 100°C, was held for 1.0 minute, was increased at 30°C/min to 200°C, was then increased at 10°C/min to 260°C, and was finally increased 20°C/min to 300°C, and was held for 8 min. Splitless injection mode was used.

Drug confirmation was performed using a Hewlett-Packard 5890 "Series 2" GC equipped with a 5972 mass selective detector. Similar chromatographic conditions to those listed above were used. The mass spectrometer (MS) was operated in the scan electron ionization mode.

## Results and Discussion

It is routine OCME protocol to test specimens from infants for volatile substances, therapeutic and abused drugs. Volatile substance testing included methanol, ethanol, acetone, and isopropanol by gas chromatography/headspace analysis. Comprehensive drug testing on the liver included color tests for salicylate and acetaminophen, a radioimmunoassay screen for morphine, and gas chromatograph/nitrogen-phosphorus detector screens for acidic drugs and 12 classes of alkaline drugs. Oxycodone was detected in the alkaline drug screen of the liver and was confirmed by full scan electron ionization gas chromatography mass spectrometry. The liver oxycodone concentration was 1.6 mg/kg; the heart blood oxycodone concentration was 0.6 mg/L. No other drugs or volatile substances were detected.

In this case, the question brought to the toxicologist was not related to the role of oxycodone to the cause of death. The cause of death in this case clearly was oxycodone intoxication. The autopsy and microscopic studies failed to identify a cause of death. There was no medical reason for the infant to be taking oxycodone. In fact, the safety and efficacy of oxycodone in pediatric patients has not been established. The Physician's Desk Reference warns that mothers taking oxycodone should not breast-feed infants (2). The mother's treating physician stated that the mother was warned against breast-feeding her infant. In adults, blood oxycodone concentrations ranging from 0.4–2.7 mg/L have been reported in cases of oxycodone intoxication (3).

The more complicated toxicologic question in this case was: how reasonable was it for an infant to be exposed to this much oxycodone solely from breast milk? A related question is, given the report by the mother that she took hydrocodone but not oxycodone on the day of the infant's death, are the toxicologic findings in this case consistent with this report? To approach this problem, a brief review of the physiology of breast milk is in order. Breast milk is synthesized in the alveolar cells of the mammary gland. It contains water, protein, electrolytes, lipids, carbohydrates, vitamins, minerals, and immune factors. Milk yields are approximately 800 mL or more per day by 6 months postpartum. The pH of the milk is slightly lower than the pH of plasma, ≈7.0–7.1. Drugs enter the milk by passive diffusion and by active transport (4).

The factors that affect the degree to which drugs enter into the milk are similar to the factors that affect the general movement of drugs within the body: degree of ionization, lipid solubility, and concentration gradient. The pKa of oxycodone, a basic drug, is 8.5. The pKa of hydrocodone is 8.9 (3). The Henderson-Hasselbach equation for basic drugs is:

$$\mathrm{pKa} = \mathrm{pH} + \log\ (\text{ionized/unionized})$$

According to this equation, the lower the pH, the greater the amount of ionized drug in the fluid. Since the pH of milk is slightly lower than that of plasma, a greater amount of ionized drug will be "trapped" in the milk. Therefore, the drug concentration of oxycodone or hydrocodone in the milk will be higher than the drug concentration in the plasma. Unfortunately, no analytical data pertaining to the plasma concentration of oxycodone or hydrocodone in the mother was available; therefore, this relationship could not be used to estimate the milk concentration of oxycodone or hydrocodone. However, given the structural and pKa similarities between the two drugs, it seems unlikely that the drug taken the previous day by the mother would be present in the milk to a greater extent than a drug taken that day. If exposure to the drug came from breast milk, it is reasonable that the hydrocodone would also be detected in the infant. Since no hydrocodone was detected in the infant, the mother's reported drug use is inconsistent with the infant's exposure to the drug via breast milk. Furthermore, no acetaminophen, the other component of Lorcet®, was detected in the infant.

One published study has reported oxycodone concentrations in breast milk. In six postpartum women administered one–two capsules of oxycodone/acetaminophen every four to seven h, maternal plasma concentrations of 0.014–0.035 mg/L were associated with milk concentrations < 0.005–0.226 mg/L. The average milk to plasma concentration ratio was 3.4, although as expected, there were large variations in the ratio. Peak milk concentrations occurred 1.5–2 h after the initial dose (5).

Average consumption of breast milk by an infant is 150 mL/kg/day (3). Since the infant in this case weighed 7.7 kg, this corresponds to a maximum daily consumption of 1.15 L of milk.

According to the mother, the infant was breast-fed three times a day; therefore, per feeding, the infant at most consumed approximately 0.4 L (about 13 oz). If the highest milk concentration referenced above were used (0.226 mg/L), this would represent a dose of 0.09 mg of oxycodone per feeding. Even if the milk oxycodone concentration was an order of magnitude higher than the highest concentration reported in the literature, this would correspond to an oxycodone exposure less than 1 mg per feeding. It is highly questionable whether the oxycodone concentrations measured postmortem in the infant can be produced solely from this exposure.

From the above discussion, we conclude that, at best, there are serious concerns about the manner in which the infant was exposed to the oxycodone in this case. Nonetheless, the medical examiner ruled that the manner of death was homicide, as the mother either purposefully administered the infant oxycodone or, through neglect, allowed the infant to be exposed to oxycodone from breast milk.

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