

Codeine Intoxication in the Neonate

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ABSTRACT. Although opiates can provide patients with relief from pain and the discomfort of cough, the routine prescription of these drugs for infants demands caution and concern. Infants, particularly neonates, are not merely small adults requiring smaller dosages, but rather uniquely different patients. Neonates present with an immature physiology and biochemistry with respect to drug metabolism. We report a case of codeine intoxication in the neonate, in which the drug was prescribed for cough control during an emergency department visit. *Pediatrics* 1999;104(6). URL: <http://www.pediatrics.org/cgi/content/full/104/6/e75>; codeine, neonate, toxicity, morphine, fatality.

CASE REPORT

Baby Z was born at 36 weeks' gestation with Apgar scores of 9 and 9. By examination he seemed to be a healthy 36-week infant with a birth weight of 6 pounds. He progressed satisfactorily and was discharged to home 2 days later.

At 29 days of age, baby Z was brought to the local hospital for evaluation of frequent cough and occasional vomiting, which had started the previous day. Physical examination at that time revealed a rectal temperature of 98.2°F, a pulse of 160, and respirations of 32. A chest radiograph showed no evidence of active cardiac or pulmonary pathology and the infant was diagnosed with an upper respiratory infection. Baby Z was discharged to home with instructions to treat with Triaminic syrup (Sandoz Consumer, East Hanover, NJ) and Pedialyte (Ross Laboratories, Columbus, OH).

The baby did not improve over the course of the day and returned to the hospital emergency department later that afternoon. Physical examination revealed a temperature of 97°F, a pulse of 160, and respirations of 28. The chest was clear, the heart was in normal sinus rhythm, and the abdomen was soft. The assessment at this time was a viral tracheitis. The patient was discharged to home with instructions to take 1 mL Novahistine DH (SmithKline Beecham Pharmaceuticals, Pittsburgh, PA) every 6 hours for 3 days (Novahistine DH contains 2 mg of codeine per milliliter, and in this infant, the dose would have

been .63 mg/kg), to discontinue the Triaminic medication, and to see the pediatrician in 2 days.

At 8 PM the baby was given a 1-mL dose of oral Novahistine DH. At 2 AM on the next day, a second 1-mL dose was given. At 3 AM, the baby seemed to be in no distress according to the mother. At 4 AM, the mother noted that the baby was unusually quiet and when she checked, the baby was not breathing. An ambulance was called, and the baby was transported to the hospital, where resuscitative efforts continued in the emergency department. Despite lifesaving measures, the patient died.

Autopsy and Toxicology Results

Notable findings at autopsy included severe bronchitis/bronchiolitis and mild bilateral pulmonary congestion.

Codeine and metabolites in postmortem samples of blood, urine, and liver extract were identified and quantitated by gas chromatography, mass spectrometry.¹ Codeine is metabolized by several mechanisms (discussed below), and the metabolites can be analyzed either as the total (the combined free drug plus the hydrolyzed conjugates) or the free drug alone. The difference between the total and free drug concentrations equals the amount of conjugated drug.² Postmortem toxicological findings are reported in Table 1.

The cause of death, determined by the chief medical examiner, was acute opiate intoxication with contributory findings of severe bronchitis/bronchiolitis.

DISCUSSION

Novahistine DH is an antitussive, decongestant, and antihistamine preparation. In each 5-mL formulation, there are 30 mg of pseudoephedrine hydrochloride, 10 mg of codeine phosphate, 2 mg of chlorpheniramine maleate, and 5% alcohol. With 2 doses of Novahistine DH, this infant received 4 mg of codeine within a 6-hour period or 1.26 mg/kg. Given the slower metabolism of codeine in infants,³ this dosage is consistent with the postmortem toxicological findings of .34 mg/L of free codeine (Table 1). Toxicological postmortem findings in the blood, urine, and liver of the infant in this case showed both codeine and its primary metabolite morphine. In addition, a trace of chlorpheniramine, an antihistamine, also was found in the blood.

Codeine is given to suppress the cough reflex by a direct effect on the cough center in the medulla. In addition, codeine provides mild analgesia and mild sedation. Intoxication results in somnolence, ataxia,

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TABLE 1. Postmortem Toxicological Findings

Heart blood	
Free morphine	None detected
Total morphine	.04 µg/mL
Free codeine	.34 µg/mL
Total codeine	.48 µg/mL
Chlorpheniramine	Trace
Urine	
Total morphine	1.3 µg/mL
Total codeine	14.10 µg/mL
Liver	
Free morphine	None detected
Total morphine	.07 µg/g
Free codeine	.43 µg/g
Total codeine	.56 µg/g

miosis, vomiting, and skin itching and can produce respiratory depression.⁴

As an opiate analgesic, codeine occurs naturally in opium and is produced commercially by 3-O-methylation of morphine. It is metabolized by conjugation to codeine-6-glucuronide and to a minor extent is biotransformed via O-demethylation to morphine and via N-demethylation to norcodeine.⁵ Codeine-6-glucuronide is the major metabolite found in urine, whereas codeine is excreted only as a small proportion of the original dose.

Many authors feel that the opiate effects of codeine are primarily attributable to morphine.⁶ The clinical observation of the increased sensitivity of infants to opiates is probably the result of drug accumulation rather than an increased receptor sensitivity to morphine.⁷ The differences in drug metabolism in the neonate and infant have been well-described⁶⁻¹³ with particular emphasis on pharmacokinetic differences between adults and neonates (preterm neonates differing from full-term neonates and children).¹⁴ These differences suggest caution and discretion in giving drugs to neonates because of the differences in these patients' rates of absorption, distribution, and metabolism of drugs, compared with those of older children or adults.

The primary metabolic pathway of glucuronidation is low at birth, and the adult level is not reached until 3 years of age.¹³ Newborns have been noted to have a reduced ability to conjugate drugs with glucuronic acid and glycine but an increased capacity to conjugate them with sulfate.¹⁵ Therefore, codeine is seldom recommended for infants <6 months of age, because the major metabolic pathway for the metabolism of codeine is not fully developed.¹⁶ In addition, the rate of morphine elimination is much slower in the neonate than in older children or adults because of lower clearance rates. This suggests that proportionally higher serum opiate concentrations are found in neonates.⁶ Longer half-lives of codeine and morphine have been found in small infants.³

Fatal cases of codeine intoxication have been reported in children.¹⁶ All reported cases involved codeine in preparations with an antihistamine and decongestant. Antihistamines, particularly the first generation histamine receptor type 1 blockers such as chlorpheniramine, contain both sedative and anticholinergic activity,¹⁷ and concomitant use with co-

deine can potentiate the effects on central nervous system depression.

Case reviews of codeine intoxication in children 1 to 6 years of age by von Muhlen Dahl and colleagues⁴ have shown that ingestion of >5 mg/kg of codeine led to respiratory failure 30 minutes to 15 hours after ingestion. They reported 2 deaths in their series, and state the importance of monitoring respiration in codeine intoxication until all symptoms have disappeared. In addition, as illustrated in this case and reported by von Muhlen Dahl,⁴ conditions that limit the ability to obtain adequate oxygenation (eg, bronchitis or bronchiolitis) may compound the respiratory depressive effects of opiates.

In fatal cases of adult codeine intoxication,⁴ the concentration range of whole blood codeine has been reported to be 1.0 to 8.8 mg/L, with whole blood morphine levels of 0 to .5 mg/L. Fatal concentrations in the liver are reported to be 0 to .5 mg/kg and 0 to 6.3 mg/kg for codeine and morphine, respectively. However, the postmortem concentration of codeine is subject to redistribution and, as a result, may vary depending on the site from which the blood is sampled. In codeine only overdose (ie, no other drug ingestion), ratios of heart to peripheral blood codeine concentrations range from 2.3 to 3.5.¹⁹

This case underscores the importance of recognizing the differences in the neonate drug metabolism, compared with the metabolism of older children and adults. The premature infant is susceptible to drug intoxication as a result of an immature enzyme system. Additional caution is advised when underlying respiratory conditions exist, because these may compound the effects of opiates and contribute to respiratory depression.

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