# Neonatal withdrawal syndrome due to maternal codeine use

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Neonatal withdrawal from maternal drugs and medications is not uncommon. Codeine-containing analgesic preparations given to pregnant mothers for headache have been identified as a cause of neonatal withdrawal syndrome. The present case highlights the importance of obtaining a detailed maternal drug history including prescription and nonprescription drugs, and highlights the need for prenatal counselling for women who are taking narcotic-containing analgesics.

**Key Words:** *Codeine; Newborn; Tylenol; Withdrawal syndrome*

## Le syndrome de sevrage néonatal lié à la consommation de codéine par la mère

Il n'est pas rare de sevrer un nouveau-né des drogues et médicaments qu'a consommés la mère. Il est établi que les préparations analgésiques qui contiennent de la codéine et qui sont données aux femmes enceintes pour soulager les maux de tête représentent une cause de syndrome de sevrage néonatal. Le présent cas fait ressortir l'importance d'obtenir les antécédents détaillés de la mère quant à ses médicaments, qu'ils soient sur ordonnance ou en vente libre, ainsi que la nécessité de donner des conseils prénatals aux femmes qui prennent des analgésiques contenant des narcotiques.

Neonatal withdrawal syndrome (NWS) is not an uncommon problem in neonatal intensive care units and is most commonly described in association with addicted mothers. It is common to prescribe analgesics during pregnancy for chronic pain disorders such as migraine or backache. Diagnosis of NWS could be delayed if a detailed history of maternal drug use is not obtained. Only a few cases have been reported in the literature regarding codeine withdrawal in neonates (1-3). NWS develops in 55% to 94% of newborns exposed to narcotics in utero, but the signs of withdrawal are nonspecific (4). We describe a newborn with withdrawal symptoms due to the mother taking an analgesic containing codeine (Tylenol 3, Johnson & Johnson Inc, USA) during pregnancy for control of pain. The present case highlights the importance of obtaining detailed medication history and prenatal counselling, particularly for pregnant women who are on prescription medication containing opiates.

## CASE PRESENTATION

A term male infant weighing 3687 g was born to a 30-year-old woman (gravida 6, para 4; four living children) by spontaneous vaginal delivery. Her maternal, prenatal and serological tests were negative, her group B streptococcus status was unknown and she had a positive urine test for *Chlamydia trachomatis* at 29 weeks, which was treated with azithromycin. She denied the use of any recreational drugs during pregnancy, and the pregnancy was otherwise uneventful. Her membranes ruptured at the time of birth and did not have any clinical signs of chorioamnionitis. The baby cried soon after birth and had Apgar scores of 9 and 9 at 1 min and 5 min, respectively. Umbilical arterial pH was 7.34 with a base excess of −3.

The baby was transferred to the neonatal intensive care unit at 1.5 h of age for jitteriness and irritability. On physical examination, no dysmorphic features were noted; his temperature was 37.2°C, heart rate was 168 beats/min, respiratory rate was 50 beats/min to 60 beats/min, blood pressure was 74/33 mmHg and he had hypertonia of all limbs. The remainder of the systemic examination was within normal limits. Preliminary investigations including blood glucose, calcium, sodium, phosphorous and a sepsis screen were normal. The mother reported a history of migraine and was taking up to six tablets a day of Tylenol 3 (acetaminophen and codeine) during the last trimester of her pregnancy. Suspecting drug withdrawal, a urine drug screen was performed and the result was positive for opiates, which were identified as codeine and its metabolites, norcodeine and morphine. Finnegan neonatal abstinence syndrome scores (5) were recorded and ranged from 14 to 22 in the first 24 h, with the scores decreasing following admission. He was treated conservatively and his symptoms and neonatal abstinence syndrome scores improved without requiring pharmacologic therapy before the final results of urine drug testing. By day 6, the baby was asymptomatic, feeding well, had gained weight and was discharged home.

## DISCUSSION

Tylenol (active ingredient acetaminophen) is a popular North American brand of medications advertised for relieving pain, reducing fever and relieving the symptoms of allergies, cold, cough and flu. There are different formulations of Tylenol on the market with various combinations of medications. The mother of this infant was taking Tylenol 3 for migraine. One tablet of Tylenol 3 contains 300 mg of acetaminophen, 15 mg of caffeine and 30 mg of codeine phosphate. The mother was taking approximately six tablets of Tylenol 3 daily, which amounted to a codeine intake of 180 mg/day.

Codeine, an opioid derivative, is a common component in analgesic and antitussive (anticough) preparations. Approximately 50% to 70% of codeine is conjugated with glucuronic acid to produce codeine-6-glucuronide in the liver (6). Approximately

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10% to 15% of codeine is N-demethylated to norcodeine by the cytochrome P450 (CYP) enzyme 3A4. Between 0% to 15% of codeine is O-demethylated to morphine, the most active metabolite, by CYP2D6, which in turn is immediately glucuronidated to morphine-3-glucoronide and, to a lesser extent, to morphine-6-glucoronide and excreted through the kidney (6). In fetal liver microsomes, codeine O-demethylation does not occur, while N-demethylation is comparable with that seen in adults (7). The rate of elimination of morphine through the kidney and liver is reduced in neonates. The average elimination half-life of codeine in children and adults is 2 h to 4 h. Neonates and infants have a longer half-life, up to 6 h, as a result of reduced glucuronidation (8,9).

The *CYP2D6* gene is highly polymorphic, and the genotype of *CYP2D6* determines the rate of metabolism of codeine. Individuals are catagorized into poor metabolizers, extensive metabolizers and ultrarapid metabolizers, depending on their *CYP2D6* genotype. Poor metabolizers are unable to convert codeine to morphine efficiently and as a consequence may not experience pain relief. Ultrarapid metabolizers may metabolize codeine too efficiently, leading to morphine intoxication. Polymorphisms of *CYP2D6* can be life threatening for some breastfed babies. A case of neonatal death due to opioid toxicity via breast milk from a mother who had been prescribed codeine for episiotomy pain has been reported (10).

We could only find a few reports of withdrawal following codeine use in nonaddicted mothers. In 1965, Van Leeuwen et al (1) described the first case of codeine withdrawal in a neonate born to a nonaddicted mother. The mother had taken between six and eight grains (389 mg to 518 mg) of codeine and between 60 to 80 grains (3888 mg to 5184 mg) of acetylsalicylic acid daily for eight weeks before delivery for breast cancer with pathological fracture and skin abscesses. The neonate was treated for the symptoms and responded well to subcutaneous codeine and phenobarbital. In 1980, Mangurten and Benawra (2) reported codeine withdrawal in two infants of nonaddicted mothers. The mothers of these infants were on cough medications that contained codeine along with other agents. In 1997, Khan and Chang (3) reported an infant born at 34 weeks' with NWS. The infant's mother had taken an analgesic with codeine, at a dose of at least 90 mg of codeine a day, for two months before delivery, for relief of severe headache and lower back pain. The diagnosis was delayed for 48 h and was made after a deeper scrutiny of maternal drug intake.

Despite the availability of several abstinence scoring systems, none has been adopted as the standard. Finnegan neonatal abstinence scoring, consisting of weighted scoring of 31 items, was used for monitoring of NWS in our unit (5). Pharmacological treatment is indicated when the total abstinence score is ≥8 for three consecutive evaluations. The indications for drug therapy include seizures, poor feeding, diarrhea and vomiting resulting in excessive weight loss and dehydration, inability to sleep and fever unrelated to infection (4).

NWS can be a life-threatening condition and can occur under situations that would not normally arouse suspicion before the onset of symptoms. The outcome of babies born to mothers with substance abuse problems has not been studied in detail. Kandall et al (11) reported increased risk of sudden infant death syndrome with opioid use. Infants exposed to opiates antenatally have an increased risk of adverse neurodevelopment, particularly cognitive and psychomotor deficits, at 18 months and three years of age (12).

With the availability of over-the-counter preparations containing larger doses of codeine, NWS may pose a more significant problem. Treatment with narcotic analgesics during pregnancy should be avoided if possible and consideration should be given to other alternatives. If this is not possible, prenatal counselling is essential with regard to the effects of the medications on the developing fetus and the propensity for NWS.

## CONCLUSIONS

A detailed maternal history including both prescription and nonprescription drugs should be taken, with clear knowledge about the components of each drug preparation. This will avoid delays in diagnosis, as well as unnecessary investigations and treatment. This would also call for recommendations to institute warning labels on codeine preparations, especially for use during pregnancy and lactation. We would like to emphasize the need for prenatal counselling for women who are on narcotic-containing analgesics.

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