Baby boy blue – why is this newborn lethargic?

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A one-week-old boy was seen in the emergency department with a two-day history of poor feeding and increasing lethargy. He was born at term after an uneventful pregnancy by repeat caesarean section. His birth weight was 3.2 kg. The patient's Apgar scores were 8 and 9, and he was discharged home on day 3 with exclusive breastfeeding. He has two older siblings: a five-year-old sister born in the mother's homeland of Sri Lanka, and a three-year-old brother born in Canada by caesarean section because of failure to progress. Both siblings and the parents are in good health, and there was no significant family history.

On examination, the baby was a term male infant, afebrile with a blood pressure of 75/45 mmHg, heart rate of 120 beats/min and shallow respirations with a rate of 16 breaths/min. He did not respond well to stimuli and had a poor suck. His physical examination was otherwise unremarkable.

A full septic workup was performed, with unremarkable results. During the process of the workup, a urine drug screen was sent, which was positive for opiates. More specific analysis revealed a serum morphine concentration of 55 µg/mL – a potentially toxic concentration. A 0.01 mg/kg dose of naloxone was administered, with good clinical improvement.

Further questioning revealed that the mother was given an acetaminophen-codeine product for analgesia postcaesarean section. She had been having increasing pain after discharge because she was caring for her newborn plus two busy older siblings. She reported taking one or two pain tablets three or four times a day, and noted excellent pain relief but also drowsiness and constipation.

Genetic testing was performed to investigate the maternal and infant pathways of codeine and morphine metabolism. The mother was shown to have a gene duplication for cytochrome P450 2D6 (CYP2D6), which classified her as an ultrarapid metabolizer. The mother was also found to be homozygous for the UGT 2B7*2 allele, a polymorphism in the glucuronidation of morphine associated with increased production of morphine 6-glucuronide, the active metabolite of morphine. This 'two-hit' genetic variation would expose her newborn to very high concentrations of morphine and the active metabolite of morphine via breast milk.

LEARNING POINTS

- Codeine is a prodrug and, by itself, has relatively poor analgesic effects (1). These effects are due to the metabolism of codeine to morphine by CYP2D6, which is further metabolized by glucuronidation to morphine 3-glucuronide (an inactive metabolite) and morphine 6-glucuronide (an active metabolite).
- Codeine and morphine undergo polymorphic metabolism (1-3), with genetically determined variability.

Codeine metabolism has three well-recognized phenotypes with respect to CYP2D6:

- Poor metabolizers: reduced enzyme activity with likely less morphine production;
- Extensive metabolizers: the most common phenotype (90% in northern European populations) with efficacy and toxicity of codeine best established; and
- Ultrarapid metabolizers: increased enzyme activity with likely markedly more morphine production (1,2).

Polymorphisms in CYP2D6 are not uniformly distributed across the world (1,2). In northern Europe, ultrarapid metabolizers make up 1% of the population, the Mediterranean 8%, and the Horn of Africa, the Middle East and South India 20% to 25%.

Polymorphisms of morphine glucuronidation have been described, favouring the production of the active metabolite versus the inactive one, which would tend to exaggerate the effects of a dose of morphine or codeine (4).

- The combination of key polymorphisms can create a 'perfect storm', in which newborns can be presented with excessive doses of morphine in the context of endogenous metabolism that favours production of an active metabolite (5,6).
- The clinical effects of opiates are not arcane (7). A careful history and physical examination, and keeping an open mind to diagnostic possibilities remain essential. This baby had the classical combination of lethargy and bradypnea associated with opiate overdose. Significantly, the mother also had complaints suggestive of opiate overdose including lethargy and constipation. It would have been easy to consider sepsis alone as a diagnosis, but had this occurred and the baby continued to be breastfed, unfortunate (and even fatal) consequences might have ensued.
- Potent drugs have potent adverse events. When prescribing opiates for women in the postpartum period

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or while breastfeeding, it is key to advise on symptoms to watch for, in themselves and in their infants, and when to seek medical advice (7). Careful follow-up needs to be assurred. Of note, the use of alternative opiates, such as oxycodone, does not prevent these problems because many opiates are metabolized by common pathways. One should also use codeine with care for other indications in children, such as for postoperative pain (8).

- If possible, during breastfeeding, codeine should not be used for longer than four days. If pain still persists, an attempt should be made to decrease the dose of codeine or switch to a nonsteroidal anti-inflammatory drug (9).
- The present case points to the future of drug prescribing. There are now assays to determine the genotype of the key pathways involved in codeine bioactivation, and studies are currently being conducted to determine the role of such testing in the personalized therapy of women postpartum. Clinicians are well advised to watch for the results of these studies.

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