Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

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In April, 2005, a full-term healthy male infant, delivered vaginally, showed intermittent periods of difficulty in breastfeeding and lethargy starting on day 7. During a well-baby paediatric visit on day 11, the paediatrician noted that the baby had regained his birthweight. On day 12, however, he had grey skin and his milk intake had fallen. He was found dead on day 13. Postmortem analysis showed no anatomical anomalies. Blood concentration of morphine (the active metabolite of codeine) was 70 ng/mL by gas chromatography-mass spectrometry (GC-MS)—neonates breastfed by mothers receiving codeine typically have morphine serum concentrations of 0–2·2 ng/mL.[1] The mother had been prescribed a combination preparation of codeine 30 mg and paracetamol 500 mg after birth for episiotomy pain (initially two tablets every 12 h, reduced to half that dose from day 2 because of somnolence and constipation). She continued the tablets for 2 weeks. Because of poor neonatal feeding, she stored milk on day 10, which was later assayed for morphine by GC-MS. A morphine concentration of 87 ng/mL was found—the typical range of milk concentrations after repeated maternal codeine is 1·9–20·5 ng/mL at doses of 60 mg every 6 h.

Genotype analysis was done for cytochrome P450 2D6 (*CYP2D6*), the enzyme catalysing the O-demethylation of codeine to morphine.[2] The mother was heterozygous for a *CYP2D6*2A* allele with *CYP2D6*2×2* gene duplication, classified as an ultra-rapid metaboliser. This genotype leads to increased formation of morphine from codeine, consistent with the somnolence and constipation she experienced.[3] The maternal grandfather, the father, and the infant had two functional CYP2D6 alleles (*CYP2D6*1/*2* genotypes), classified as extensive metabolisers. The maternal grandmother was an ultra-rapid metaboliser.

The clinical and laboratory picture is consistent with opioid toxicity leading to neonatal death. Most of the analgesic and central-nervous-system depressant effects of codeine are secondary to its metabolism to morphine by CYP2D6.[2] Neonates invariably have impaired capacity to metabolise and eliminate morphine. Codeine is a commonly used analgesic after labour for pain associated with episiotomy and caesarean section. The American Academy of Pediatrics lists codeine as compatible with breastfeeding, despite lack of sufficient published data to support this recommendation.[4] This case shows that polymorphism of *CYP2D6* can be life threatening for some breastfed babies. Given that the frequency of *CYP2D6* ultra-rapid metaboliser genotypes ranges from 1% in Finland and Denmark to 10% in Greece and Portugal, and 29% in Ethiopia, this polymorphism is clinically important.[5] Several strategies can be considered to prevent life-threatening neonatal toxicity (table). Careful follow-up of breastfeeding mothers using codeine, and their infants, may be a useful approach. Testing of mother–child pairs when the mother or neonate is experiencing symptoms consistent with opioid toxicity may be necessary—eg somnolence, or poor milk intake. The facilities to measure morphine concentrations are not routine in most hospitals; in any suspicious case, naloxone can reverse, and, therefore, corroborate opioid toxicity. Above all, avoidance of codeine use during breastfeeding, with its use being retained as second or third line for uncontrolled pain, could also avert this situation. Whatever clinical approach is taken, codeine cannot be considered as a safe drug for all infants during breastfeeding.

References

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Action	Advantages	Disadvantages
Avoid codeine when breastfeeding; use paracetamol or non-steroidal anti-inflammatory drugs	Avoids potential neonatal toxicity	Potential uncontrolled maternal pain
Avoid high-dose codeine (240 mg daily) for more than a few days	Minimises potential neonatal toxicity	Suboptimal maternal pain control Dose may still be too high a dose for ultra-rapid metabolisers
Avoid breastfeeding when taking codeine	Avoids potential neonatal toxicity	Loss of the benefits of breastfeeding
Inform and monitor mother and baby for signs of opioid toxicity	Ability to intervene early and prevent serious toxicity	Parental anxiety and false positive identification of toxicity
Genotype mother for CYP2D6	Predicts mothers at risk of producing excess of morphine	Expensive Not presently routine

Table: **Clinical strategies to manage breastfeeding while on codeine**