Q&A 188.5X

Codeine and breastfeeding: Is it safe and what are the alternatives?

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Background

Codeine is a weak opioid analgesic obtained from opium (1). It is considered a pro-drug displaying no analgesic properties itself. Codeine is partly metabolised in the liver by CYP2D6 (an isoenzyme of cytochrome P450) to one of its active metabolites, morphine (2). Codeine is also metabolised by the enzyme UGT2B7 to its other active metabolite codeine-6-glucuronide. DNA polymorphisms have been identified in the genes encoding a number of P450 enzymes including CYP2D6, and also the enzyme UGT2B7, which result in wide interindividual variations in drug clearance (3). These polymorphisms have implications on the efficacy and side-effects seen following codeine use, and may influence the amount of codeine and its active metabolites in the breast milk and therefore the safety of codeine use by breastfeeding mothers.

Until recently, codeine was considered the preferred opioid for use in breastfeeding mothers. However there has been a fatal case of morphine toxicity in a breast-fed infant following maternal use of codeine (4). Based on this fatality, the Medicines and Healthcare Products Regulatory Authority (MHRA) and European Medicines Agency (EMA) have contraindicated its use in women who are breastfeeding (5,6). Therefore, codeine use is no longer being recommended for this patient group.

Breastfeeding women may need short term analgesia during the post-partum period and this raises the question of suitable alternatives to codeine.

Answer

Any advice and recommendations that follow relate to full term and healthy infants. If the infant is pre-term, of low birth weight or has any medical problems, then specialist advice should be sought.

Amount of codeine in breast milk

Using data from two small studies (7,8) about the passage of codeine and morphine into breast milk following maternal doses of codeine 60mg, it can be calculated that infant ingestion is in the range of 5 to 47 micrograms/kg/day codeine or 0.3 to 3.1micrograms/kg/day morphine.

In one early study, breast milk samples were taken 2–4 hours after doses of 32 or 65mg codeine in five lactating women. No codeine was detected in any of the five samples (9).

In a further study, codeine and morphine levels were determined in the breast milk of 7 mothers and the plasma of 11 breastfed infants aged 1 to 5 days old following maternal doses of codeine 60mg. Milk codeine levels ranged from 33.8 to 314 nanograms/ml at 20–240 minutes after codeine administration; morphine levels ranged from 1.9 to 20.5 nanograms/ml. Infant plasma samples 1–4 hours after feeding had codeine levels ranging from <0.8 to 4.5 nanograms/ml; morphine levels ranged from <0.5 to 2.2 nanograms/ml (7). The authors report that the amount of morphine detected in these samples was much lower than the morphine levels of 10 to 154 nanograms/ml observed in sick neonates four hours after a therapeutic dose of 0.1mg/kg given intravenously. No episodes of apnea or bradycardia were seen in the breastfed infants..

In another small study, two lactating mothers were given a single codeine dose of 60mg. In subject 1, maximal codeine breast milk concentration was 455 nanograms/ml at 1 hour post dose; morphine breast milk concentration was 16 nanograms/ml at 1 hour, increasing to 22 nanograms/ml and remaining steady in the final sample at 12 hours. Samples were taken up to 48 hours in subject 2, in whom breast milk levels of morphine and codeine showed a similar pattern to subject 1 up to 12

hours. Morphine levels started falling at around 14 hours and fell steadily thereafter, being undetectable at 48 hours (8).

Adverse effects in breastfed infants following exposure to codeine in the breast milk

There have been several reports of adverse effects in breastfed infants following maternal use of codeine. These include bradycardia, respiratory depression, lethargy, drowsiness, poor feeding, cyanosis, and infant death (4, 10-12).

A one-week-old infant was evaluated for conjunctivitis and in the process found to have bradycardia. The mother had ingested a single 30mg dose of codeine six days earlier. The infant's heart rate normalized over 24 hours and remained stable over the next few months. The infant had previously suffered neonatal unconjugated hyperbilirubinaemia. The authors concluded that the infant may have had excessive amounts of opioid in the blood due to immature hepatic enzyme activity and this led to the depressive effect on the heart (10).

A further study reported four cases of neonatal apnea following maternal use of codeine. All infants had been born by caesarian section after 35 to 40 weeks gestation and were healthy and well until days 4 to 6 post delivery. All mothers had been breastfeeding and had been receiving codeine 60mg every 4 to 6 hours for analgesia. Codeine was discontinued and breastfeeding withheld. Resolution of the apnoea occurred over 24 to 48 hours (11).

A cohort study of 72 mother-infant pairs also found a higher risk of infant CNS depression with higher maternal doses, and 17 of these infants (24%) were reported to have CNS depression. Two of these mothers were found to be CYP2D6 ultrarapid metabolisers. One of these cases is described above, which led to the infant fatality. The other case reported to take 120mg of codeine daily. Her breastfed infant was described as extremely drowsy and feeding poorly. By day 7 post delivery, the infant had been completely switched to formula feed and symptoms had completely reversed. In addition, the cohort study showed good concordance between maternal and infant CNS depression (13).

The main focus of codeine risk has been on one case report of a fatality where much higher amounts of morphine were detected in an infant whose mother was taking codeine (4). A full-term healthy male infant showed intermittent periods of difficulty in breastfeeding and lethargy starting on day 7. On day 12, he had grey skin, milk intake had fallen and on day 13 he died. The mother, who was later found to be an ultrarapid metaboliser for CYP2D6 converting codeine to morphine to a greater extent than standard metabolisers, had been prescribed paracetamol and codeine after birth for episiotomy pain and had taken 60mg codeine twice a day for two days then 30mg twice daily for a further nine days. Milk and infant serum concentrations of morphine were much higher than expected given the maternal dose, and it was concluded that the infant died of opioid toxicity..

Metabolism of codeine and role of CYP2D6

Codeine is metabolised in the liver by CYP2D6 (an isoenzyme of cytochrome P450) to its active metabolite morphine (2).

The CYP2D6 isoenzyme is polymorphic, with individuals classified according to one of four levels of activity: poor metabolisers, intermediate metabolisers, extensive metabolisers and ultrarapid metabolisers (14). Individuals with duplication or multiduplication of the CYP2D6 gene are called ultrarapid metabolisers (15).

Opioid toxicity has been seen following single doses of tramadol and codeine taken by adults who were later found to be ultrarapid metabolisers of CYP2D6 (16,17). Conversely, analgesic efficacy may be impaired in patients who are poor metabolisers of codeine (1). It therefore follows that the ability of the mother to metabolise codeine to its active metabolite morphine may influence the risk of side effects in both mother and her breastfed infant. In addition, immature neonatal hepatic enzyme function in newborns and young infants will result in accumulation of opioids and increased risk of adverse effects.

Significant interethnic differences in CYP2D6 allele frequencies have been demonstrated from studies across many countries (3). However, no ethnic group is risk free from being an ultra-rapid metaboliser of CYP2D6.

The fatal case of morphine toxicity in a breastfed infant following maternal use of codeine shows that the presence of maternal ultrarapid metabolism of CYP2D6 can be life threatening for some breastfed infants (4). At present it is not practical to identify ultrarapid metabolisers by genotyping as current assays are complex and expensive (18), therefore we can only rely on close monitoring of breastfed infants to detect any problems.

Alternative analgesics to codeine

1. Paracetamol

Paracetamol is a non-opioid analgesic, taken to relieve mild to moderate pain and pyrexia. It can be prescribed, but is also available as an over-the-counter medicine. Paracetamol can also be given therapeutically to infants from birth, including premature infants from 28 weeks postmenstrual age. The risk to the breastfed infant of administering paracetamol to its mother is low on the basis that the quantity of drug that passes into milk is very small; representing only a small proportion of a normal therapeutic infant dose, and it also has a relatively short elimination half-life. The balance of evidence suggests that the amounts secreted into breast milk are too small to be hazardous, except the possibility of a hypersensitivity reaction, and that paracetamol should be considered the analgesic of choice during breastfeeding (19)

2. Non-Steroidal Anti-inflammatory Drugs (NSAIDs)
There is very limited information on the use of NSAIDs during breastfeeding. However, due to the extensive safe use of ibuprofen and diclofenac during breastfeeding in clinical practice, these are the preferred choices (20).

2.1 Ibuprofen
Ibuprofen is a NSAID used to relieve pain and inflammation. It can be given to infants aged one month at a dose of 5mg/kg body weight 3–4 times daily for pain, inflammation of soft-tissue injuries, and pyrexia, although this is off-label under 3 months. Ibuprofen can be prescribed, but is widely available as an over-the-counter (OTC) medicine.

Ibuprofen is considered safe for breastfeeding infants as only very small quantities appear to be excreted into breast milk after maternal ingestion (21).

2.2 Diclofenac
Limited data suggests that the levels of diclofenac in breast milk are low. Diclofenac was undetectable (<100 micrograms/L) in the breast milk over a 6-hour period after a 50 mg intramuscular injection in 6 women (22).

Six mothers were given oral diclofenac 100 mg daily orally for one week postpartum. The drug was undetectable(<10 micrograms/L) in milk of any of 59 samples of milk collected (collection times unspecified).(23). Furthermore, a woman treated with 150 mg daily of diclofenac had a breast milk diclofenac level of micrograms/L, equivalent to about 0.03 mg/kg daily for the infant (24).

Based on these low levels in breast milk, short-half life and extensive experience of safe use during breastfeeding, diclofenac is considered safe for breastfeeding mothers, assuming there is no other contraindication to its use.

3. Weak Opioid Analgesics

Several opioid analgesics are metabolised in the liver by CYP2D6 (an isoenzyme of cytochrome P450) to active metabolites.

3.1 Dihydrocodeine

There is no published evidence of safety of dihydrocodeine use by a breastfeeding mother. However extensive anecdotal experience supports its safe use (20).

Dihydrocodeine is metabolised in the liver by CYP2D6, to dihydromorphine, which has potent analgesic activity, however, unlike codeine which is pro-drug displaying no analgesic properties itself, the analgesic effect of dihydrocodeine appears to be mainly due to the parent compound (1) and is largely unaffected by an individuals metabolising capacity (25).. However, there is no data to confirm whether polymorphism of CYP2D6 has implications on potential side effects following dihydrocodeine use, and ultimately the safety of dihydrocodeine use by a breastfeeding mother.

Therefore, until more data is available regarding the metabolism of dihydrocodeine, use by a breastfeeding mother should be at the lowest effective dose for the shortest duration. As it is not practical to genotype all breastfeeding mothers and infants to predict side effects, we can only rely on monitoring the infant to detect any potential problems. All breastfed infants should be monitored for opioid adverse effects regardless of the maternal dose. If significant opioid adverse effects develop in the mother, this could suggest the possibility that she is an ultrarapid metaboliser and that the risk of adverse effects in the infant may be increased.

3.2 Tramadol

Tramadol is metabolised by N- and O-demethylation via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6 and glucuronidation in the liver. The metabolite O-desmethyltramadol is pharmacologically active (1). In a pharmacokinetic study of immediate-release tramadol in healthy patients, O-desmethyltramadol concentrations were decreased by 40% in poor metabolisers compared with extensive metabolisers, suggesting that efficacy and safety may be affected by DNA polymorphisms in the genes encoding a number of P450 enzymes including CYP2D6.

Twelve women, 3-7 days postpartum, were administered 100mg intravenous tramadol as a single dose. Milk samples were collected over the following 16 hours. Results indicated that an infant would ingest 0.1% of the mother's tramadol dose (26).

One mother was taking oral tramadol 1800 mg daily during pregnancy and postpartum for chronic back pain. On approximately day 3 postpartum (time not specified), the breast milk concentration of tramadol was 1.8 mg/L (27).

Seventy-five mothers who were 2 to 4 days postpartum provided 3 milk samples from both breasts during the 6 hours following a dose of 100 mg of oral tramadol after taking at least 4 doses. The average milk concentration of tramadol was 748 micrograms /L (range 681 to 815 micrograms /L) and of its active metabolite, O-desmethyltramadol, was 203 micrograms /L (range 188 to 217 micrograms /L). These values translate to an average infant dosage of 112 and 30 mcg/kg daily of the drug and metabolite, respectively. An exclusively breastfed infant would receive maternal weight-adjusted dosages of 2.24% of tramadol and 0.64% of its metabolite. No behavioural adverse effects were observed in the breastfed infants (28). The same dataset was reanalysed after separating mothers into CYP2D6 poor and extensive metabolisers. The relative and combined infant dose remained below the suggested 10% threshold for drugs in breast milk, irrelevant of metabolising capacity of the mother (29).

Detectable levels (>12 micrograms/L) of tramadol were found in samples of breast milk collected 10 hours after a 50 mg maternal dose of intravenous or oral tramadol. No other clinical details or milk levels were reported (30).

There is one case report where an adult patient took a single 100mg dose of tramadol and developed ataxia, dilation of the pupils, numbness and dysphoria lasting approximately 4 hours. The patient was phenotyped for CYP2D6 activity, and was determined to be an extensive metaboliser with very high CYP2D6 activity. The authors suggested the reaction may be due to high concentrations of the active O-desmethyl metabolite of tramadol (16).

Tramadol use by a breastfeeding mother is considered acceptable based on low levels in breast milk when prescribed at the lowest effective dose for the shortest duration. As it not practical to

genotype all breastfeeding mothers and infants to predict side effects, monitoring should be undertaken as discussed for dihydrocodeine above.

Summary

♦   Until recently, codeine was considered the preferred opioid for use in breastfeeding mothers. However a fatal case of morphine toxicity in a breastfed infant following maternal use of codeine has lead the MHRA and EMA to contraindicate its use by breastfeeding women.

♦   Paracetamol should be considered the analgesic of choice during breastfeeding, as the risk to a breastfed infant is low based on the quantity of drug that passes into milk is very small; representing only a small proportion of a normal therapeutic infant dose.

♦   Where paracetamol alone is ineffective, use of a NSAID should be considered. Ibuprofen and diclofenac, unless contraindicated for other reasons, produce low levels in breast milk and are the preferred NSAIDs for use in breastfeeding mothers.

♦   Weak opioids, specifically dihydrocodeine or tramadol, can be considered for a breastfeeding woman. This should be at the lowest effective dose and for the shortest duration. Regular use of any opioid beyond 3 days should be under close medical supervision.

♦   If significant opioid adverse effects develop in the mother, this could suggest the possibility that she is an ultrarapid metaboliser and that the risk of adverse effects in the infant may be increased. All breastfeeding mothers, regardless of ethnicity, should be informed of the potential problems and advised to stop breastfeeding if symptoms develop and seek medical advice.

♦   If opioids are prescribed and adverse effects develop in breastfeeding infants, the possibility of opioid toxicity should be considered regardless of the maternal dose. In such cases, the opioid should preferably be replaced by an alternative non-opioid analgesic and breastfeeding interrupted until the cause of the symptoms is clear.

♦   Neonates and young infants are at the most risk from the adverse effects of opioids due to their immature hepatic enzyme function and therefore extra caution should be taken in infants less than 2 months of age. The elimination of morphine is much more rapid in infants over 2 months.

Limitations

This review is presented for general guidance. Many decisions as to the safety of analgesic regimens will need to be taken on a case-by-case basis, particularly if there are unusual circumstances e.g. premature infants, infant morbidity, requirement for high doses, concurrent medication etc. In these instances, further advice can be sought from the UK Drugs in Lactation Advisory Service (UKDILAS) provided by the Trent and West Midlands Medicines Information Services (Telephone: 0116 258 6491 or 0121 311 1974).

Evidence for the clinical relevance of CYP2D6 genotype is not based on prospective studies but rests largely on case reports, extrapolation of blood drug levels to effect, small pharmacokinetic and pharmacodynamic studies and retrospective analyses.

The extent of metabolism of codeine by enzyme UGT2B7 to its other active metabolite codine-6-glucuronide is also subject to genetic variability, which can also alter the amount of active narcotic in the breast milk. However, studies have not measured the amount of codeine-6-glucuronide in the breast milk and the effect this may have on the breastfed infant.

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Search strategy
Please specify which of these are used if appropriate, (whether or not all of them yielded useful information) and add others if necessary:

- Embase (search terms: codeine, lactation, breastfeeding, breast milk, infant feeding, colostrum, genetic polymorphism, cytochrome-P450-2D6, ultrarapid metaboliser)
- Medline (search terms: codeine, lactation, breastfeeding, milk-human, breast milk, ultrarapid metaboliser, polymorphism-genetic)
- UK Drugs in Lactation Advisory Service Database (search: codeine) and specialist texts
- Professor Ann K Daly. Pharmacogenetics Group. School of Clinical and Laboratory Sciences. University of Newcastle Medical School [email 15/12/2006]
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