PHARMACOGENOMICS: CODEINE AND BREASTFEEDING

Codeine's analgesic properties are the result of its metabolism by the enzyme cytochrome P450 2D6 (CYP 2D6), which is coded by a highly variable (polymorphic) gene with over 80 variant alleles that contribute to enzyme activity. A functional gene duplication results in an ultra-rapid metabolizer (UM) phenotype and consequently higher plasma concentrations of the active metabolite, morphine. Two alleles with no activity result in a poor metabolizer (PM) phenotype and these individuals receive little to no therapeutic benefit from codeine.

Women who are UMs of codeine will have significantly higher than normal levels of morphine in breast milk and thus potentially problematic or lethal levels in their newborn. Central nervous system (CNS) depression in the infant appears to worsen after 4 days, likely because of the accumulation of morphine with continued breastfeeding. **Analgesics other than codeine (e.g. non-steroidal anti-inflammatory drugs (NSAIDs)) are recommended for use by nursing mothers. If codeine is necessary, it should not be used for longer than 4 days[1].** While maternal genotyping could be considered before codeine is prescribed, education about the signs of CNS depression in the infant might be an equally important preventive approach.

HOW DOES MY PATIENT'S GENOTYPE AFFECT HIS/HER DRUG RESPONSE?

Pharmacogenomics, or the interaction between drugs and a person's genetic makeup, is a relatively new field.

Cytochrome P450 enzymes are responsible for the oxidative metabolism of most medications. Variation in the activity of these enzymes and therefore drug metabolism is due to both environmental and genetic factors. CYP 2D6 is one of the Cytochrome P450 superfamily of enzymes. It is involved in the metabolism of a number of medications, many used for treatment of psychiatric, neurologic and cardiovascular diseases. These include medications such as fluoxetine, paroxetine, amitryptiline, olanzapine, amiodarone, propranolol, metoprolol and codeine. CYP 2D6 is part of a minor pathway in the metabolism of codeine (10%) but is the key pathway for analgesic effect[2]. ***Functional duplications*** of *CYP 2D6*, leading to enhanced codeine to morphine metabolism (ultra-rapid metabolism - UM) and associated adverse events, are seen in 2-40% of individuals depending on ethnicity[1]. North African, Ethiopian and Arab populations have the highest estimated prevalence[3]. Conversely, two CYP 2D6 alleles exist with no activity (poor metabolizer (PM) phenotype) leaving individuals with little or no therapeutic benefit from codeine.

Codeine metabolism is also modified by single nucleotide polymorphisms (SNPs) in other genes, which may result in increased drug sensitivity and adverse reactions (*ABCB1, COMT*) or decreased opioid toxicity (*OPRM1*). Screening for these polymorphisms is not routine and further investigation is needed into their importance in morphine effectiveness.[1]

In contrast to codeine, most drugs that are metabolized by CYP 2D6 are actually *deactivated*. For such drugs, like metoprolol, PM's would have enhanced drug effect and adverse drug reactions, whereas UM's would have decreased drug effect at conventional doses.[4]

Codeine, Breastfeeding and Genetics

Women who are ultra-rapid metabolizers of codeine will have significantly higher than normal levels of morphine in breast milk which could consequently cause problematic or lethal levels in the newborn. Central nervous system (CNS) depression in the infant appears to worsen after 4 days, likely because of the accumulation of morphine with continued breastfeeding. Evaluation of scientific evidence following a case report of fatal CNS depression in a breastfed infant due to morphine overproduction by a UM mother led Motherisk to suggest guidelines for safe use of medications that contain codeine during breastfeeding.[5] These include having the baby examined by a healthcare provider if not feeding well, not waking to be fed, not gaining weight or appearing limp,

and "advice to use the lowest codeine dose for no longer than four days and to switch to a non-opioid when possible" among others[1,5]. One study has shown that the neonatal safety of maternal codeine use can be improved using these Motherisk guidelines, even in those at high genetic risk for toxicity[5].

It is recommended that analgesics other than codeine be used by nursing mothers. If codeine is necessary, it is preferable that it not be used for longer than 4 days. If post-partum pain persists, an attempt should be made to decrease the codeine dose or to switch to non-codeine painkillers (e.g. non-steroidal anti-inflammatory drugs (NSAIDs)). A systematic review of all randomized trials suggests that codeine is not superior to NSAIDs for analgesia after laparotomy.[1]

While maternal genotyping could be considered before codeine is prescribed, choice of an alternative analgesic and patient education about the signs of CNS depression might be equally important preventive approaches[1]. It is not practical at this time to test every patient for whom codeine is prescribed.

RED FLAGS TO CONSIDER GENETIC TESTING OR GENETIC CONSULTATION

Genetic testing for genes influencing drug metabolism is not yet standard practice, but may be available in the future and could be considered following cases of severe adverse drug reaction.

WHAT DOES THE GENETIC TEST RESULT MEAN?

A few US laboratories offer testing for variants in a number of Cytochrome P450 genes. Such testing could identify patients liable to have either adverse drug reactions or reduced drug efficacy, which may help to determine which drug to prescribe and at what dosage.

Interpretation and use of such testing should be interpreted with caution as:

- Other medications may act as inhibitors or inducers of a drug's metabolism
- Some drugs are metabolized by a number of enzymes
- In the specific example of codeine metabolism, maternal and neonatal morphine clearance also play an important role in neonatal morphine accumulation[6]

For a recent article on codeine and breastfeeding see Kelly LE, *et al*. A clinical tool for reducing central nervous system depression among neonates exposed to codeine through breast milk. *PloS one* 2013; 8(7):e70073 and Madadi P, *et al*. Guidelines for maternal codeine use during breast feeding. *CFP* 2009;55: 1077-8

See www.geneticseducation.ca for how to connect to your local genetics centre.

References

[1] Kelly LE, *et al*. A clinical tool for reducing central nervous system depression among neonates exposed to codeine through breast milk. *PloS one* 2013; 8(7):e70073

[2] Dayer P, *et al.* Bioactivation of the narcotic drug codeine in human liver is mediated by the polymorphic monoozygenase catalyzing debrsoquine 4-hydroxylation (cytochrome p-450 dbl/bufl).*Biochen Boiphys Res Commun* 1988;152(1):411-6

[3] Health Canada Advisory – 2008-164 October 8, 2008.

[4] Weinshilboum R. Inheritance and drug response. *NEJM* 2003; 348;6: 529-37

[5] Madadi P, *et al*. Guidelines for maternal codeine use during breast feeding. *CFP* 2009;55: 1077-8

[6] Willmann S, *et al.* Risk to the breast-fed neonate from codeine treatment to the mother: a quantitative mechanistic modeling study. *Clin Pharmacol. Ther.* 2009;86(6):634-43

Other resources:

Motherisk www.motherisk.org

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Updated from the original Gene Messenger developed for the GenetiKit research project.
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