PHARMACOGENOMICS: CODEINE AND BREASTFEEDING

Bottom line: Codeine's analgesic properties are the result of its metabolism by the enzyme cytochrome P450 2D6 (CYP2D6), which is coded by a highly variable (polymorphic) gene with over 100 variant alleles that contribute to enzyme activity.[1] 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.

Individuals 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 newborns. 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 individuals. If codeine is necessary, it should not be used for longer than 4 days.[2]** While 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 THEIR 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. CYP2D6 is one of the cytochrome P450 superfamily of enzymes. It is involved in the metabolism of a number of medications, many used for the treatment of psychiatric, neurologic and cardiovascular diseases. These include medications such as fluoxetine, paroxetine, amitriptyline, olanzapine, amiodarone, propranolol, metoprolol and codeine. CYP2D6 is part of a minor pathway in the metabolism of codeine (10%) but this is the key pathway for analgesic effect.[3] ***Functional duplications*** of *CYP2D6*, leading to enhanced codeine to morphine metabolism (ultra-rapid metabolism - UM) and associated adverse events, are seen in 2-40% of individuals.[2] There is considerable ethnic variation, with North Africans, Arabs and Ethiopians (29%) having the highest estimated prevalence, and modest rates in the Oceanian (21%) and Ashkenazi Jewish (11.5%) populations.[1,4,5] Conversely, two *CYP2D6* 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.[2]

In contrast to codeine, most drugs that are metabolized by CYP2D6 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.[6]

Codeine, Breastfeeding and Genetics

Individuals 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. A systematic review of all randomized trials suggests that codeine is not superior to NSAIDs for analgesia after laparotomy.[2] Therefore it is recommended that, where possible, analgesics other than codeine be used by nursing individuals. If codeine is necessary, guidelines for safe use during breastfeeding should be followed.[7] The lowest possible dose should be chosen, and taken for no longer than 4

days.[2,7] If post-partum pain persists, an attempt should be made to decrease the codeine dose or to switch to a non-codeine painkiller if possible.[2,7] In addition, the baby should be examined by a healthcare provider if not feeding well, not waking to be fed, not gaining weight or appearing limp. One study has shown that the neonatal safety of codeine use during breastfeeding can be improved using these guidelines, even in those at high genetic risk for toxicity.[7]

While 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.[2] 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[8]

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

References

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