GENE MESSENGER

☆ Topic: Codeine and Breast Feeding

☆ **Summary:** Some women take normal doses of codeine but convert more codeine into the active metabolite morphine than expected. Genetic testing may indicate that these women are ultra-rapid metabolizers of the drug. This would result in significantly higher than normal levels of morphine in breast milk and consequently could cause problematic or lethal levels in the newborn.

Pharmacogenomics, or the interaction between drugs and a person's genetic makeup, is a relatively new field. Drug metabolism can be influenced by genetic variation as well as by other drugs or environmental factors. The clinical application of pharmacogenetic testing is still limited. It is not practical at this time to test every patient for whom codeine is prescribed. Even though most women metabolize codeine at the normal rate, other analgesics such as nonsteroidal anti-inflammatory drugs should generally be used by breast feeding women.

☆**Bottom line:** It is recommended that analgesics other than codeine be used by nursing mothers. Nursing mothers on codeine should minimize the duration of therapy and monitor their babies for signs of respiratory depression. Genetic testing for drug metabolizer genes is not yet standard practice, but may be available in the future and could be considered following cases of severe adverse drug reactions.

✓ The Disease

- Pharmacogenomics: The genetic influence on drug metabolism and response.
- 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.

✓ The Genes

- CYP2D6 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, amitriptyline, olanzapine, amiodarone, propranolol and codeine.
- CYP2D6 is part of a minor pathway in the metabolism of codeine (10%) but is the key pathway for analgesic effect.[1]
- CYP2D6 gene function varies among different ethnic groups. The chance of being an ultra-rapid metabolizer (genotype CYP2D6) prevalence is 1/100 for those of Chinese, Japanese and Hispanic descent, 3/100 for African Americans, 1/10 to 1/100 for Caucasians, and 16/100 to 28/100 for those of North African, Ethiopian and Arab descent.[2]

✓ Consequences of having a faulty gene

- Some genetic variations in CYP2D6 lead to little or no enzyme activity. People with these variants are known as poor metabolizers (PM).
- Other people have multiple copies of CYP2D6 leading to increased metabolism. These people are referred to as ultra rapid metabolizers (UM).
- Most drugs that are metabolized by CYP2D6 are deactivated. PMs would have enhanced drug effect and adverse drug reactions. UMs would have decreased drug effect at conventional doses.

- A few drugs metabolized by CYP2D6 are converted into an active compound (e.g., codeine is converted to morphine). PMs do not get the expected degree of analgesic effect. UM's would experience increased pharmacologic effect.[3]

✓ Testing - for the faulty gene

- Testing is available through US labs that look for genetic variants in a number of Cytochrome P450 genes. This testing is not standard practice, but could be considered following cases of severe adverse drug reactions.

✓ Benefits of genetic testing

- Identification of patients who may have adverse drug reactions
- May help to determine which drug to prescribe and at what dosage

✓ Pitfalls - Watch out for…

- Maternal and neonatal morphine clearance also play an important role in morphine accumulation in the neonate.[4]
- There are additional factors such as other medications that act as inhibitors or inducers of a drug's metabolism.
- Some drugs are metabolized by a number of enzymes so there may be alternate pathways for metabolism making predicting drug metabolism even more complex.

☆References:

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☆Review Articles:

1. Madadi P, Moretti M, Djokanovic N, et al. Guidelines for maternal codeine use during breast feeding. *Canadian Family Physician* 2009;55:1077-8.
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GenetiKit KNOWLEDGE IN TRANSLATION

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