



NATIONAL PBM BULLETIN

October 9, 2007

DEPARTMENT OF VETERANS AFFAIRS (VA) VETERANS HEALTH ADMINISTRATION (VHA)
NATIONAL PHARMACY BENEFITS MANAGEMENT STRATEGIC HEALTHCARE GROUP (PBM),
MEDICAL ADVISORY PANEL (MAP), CENTER FOR MEDICATION SAFETY (VA MedSAFE), & VA WOMEN'S HEALTH GROUP

Codeine Use in Breastfeeding Women

- I. **ISSUE** – Use of codeine in certain breastfeeding mothers who are ultra-rapid metabolizers of the drug may increase the risk of serious side effects due to morphine overdose in nursing infants.
- II. **BACKGROUND** – The Food and Drug Administration (FDA) issued an Alert and Public Health Advisory regarding the use of codeine in nursing women who are ultra-rapid metabolizers of the drug. Certain individuals with a specific genotype of cytochrome P450 2D6 (CYP2D6) more rapidly and completely metabolize codeine to morphine. The result in nursing mothers is elevated levels of morphine in the serum and breast milk, which can then be transferred to the nursing infant. The estimated prevalence of this genotype varies widely by ethnic group: 1-10% Caucasians; 3% African Americans; 1% Chinese/Japanese; 1% Hispanics; 16-28% North Africans, Ethiopians, and Saudi Arabians. Although there is an FDA cleared test for determining an individual's CYP2D6 genotype, there is limited information available regarding its applicability to accurately predict codeine metabolism, and it is not routinely used in clinical practice.
- A recently published case report described a healthy 13 day old infant who died from morphine overdose. The mother was taking 60 mg of codeine every 12 hours for episiotomy pain, which she reduced to 30 mg every 12 hours after 2 days. The infant showed symptoms of difficulty breastfeeding, lethargy, and low milk intake prior to his death. Significantly elevated levels of morphine were noted in the infant's blood as well as in the mother's breast milk. The mother was later genotyped and classified as an ultra-rapid metabolizer. A search of the FDA adverse events reporting database for similar cases of morphine overdose in nursing infants revealed two cases; however, both cases were associated with additional contributing factors.
- III. **DISCUSSION** – Codeine is commonly used for pain and other medical conditions following childbirth. The American Academy of Pediatrics (AAP) classifies codeine as compatible with breastfeeding, and reports of serious adverse events in infants are rare. In most situations, it is unknown whether or not someone is an ultra-rapid metabolizer of codeine. At the request of the FDA, manufacturers of codeine-containing products will be expected to update their label to include information on differences in metabolism and concerns in breastfeeding.
- IV. **RECOMMENDATIONS** – *PBM and VAMedSAFE concur with FDA MedWatch Safety recommendations:*
- Providers should be aware of the potential risks to the infant when codeine is used by a nursing mother who is an ultra-rapid metabolizer.
 - Providers should read and follow the prescribing information for codeine-containing products and use the lowest effective dose for the shortest duration of time.
 - When codeine is used, monitor nursing mothers and their infants for signs and symptoms of opioid overdose, since it is generally not known whether individuals are ultra-rapid metabolizers.
 - Counsel breastfeeding mothers using codeine to monitor for signs and symptoms of opioid overdose in their infants (i.e., increased sleepiness, difficulty breastfeeding, breathing difficulties, or limpness) and to contact the pediatrician or seek medical attention immediately should any of these symptoms occur.
 - Inform the infant's doctor about the mother's use of codeine.
 - Consider alternatives to codeine in nursing mothers known or suspected to be ultra-rapid metabolizers (for treatment of pain, ibuprofen or acetaminophen are considered by the AAP to be compatible with breastfeeding).
 - Report adverse events to VHA's Adverse Drug Event Reporting Program and/or FDA's MedWatch program.

References:

1. Committee on Drugs. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001;108:776-89.
2. FDA Center for Drug Evaluation and Research. Information for healthcare professionals: use of codeine products in nursing mothers. www.fda.gov/cder/drug/InfoSheets/HCP/codeineHCP.htm (accessed 8/31/07).
3. FDA Center for Drug Evaluation and Research. FDA Public Health Advisory: use of codeine by some breastfeeding mothers may lead to life-threatening side effects in nursing babies. www.fda.gov/cder/drug/advisory/codeine.htm (accessed 9/19/07).
4. Koren G, Cairns J, Chitayat D, et al. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet*. 2006;368:704.