Genetic Transmission of Cytochrome P450 2D6 (CYP2D6) Ultrarapid Metabolism: Implications for Breastfeeding Women taking Codeine

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Abstract: The pro-drug codeine is commonly prescribed for postpartum pain relief in North America. The safety of codeine during breastfeeding is related in part to the extent of the active morphine metabolite catalyzed from codeine via the cytochrome P450 2D6 (CYP2D6) enzyme. In mothers who have greater than two functional copies of the CYP2D6 gene (CYP2D6 ultrarapid metabolism phenotype; UM) a substantially higher proportion of morphine is produced. Label changes on codeine-containing medications will highlight the risks associated with this genotype for breastfeeding mothers, but are not supported by translation strategies on how to incorporate this pharmacogenetic knowledge into clinical practice. To address the immediate issue of CYP2D6 UM inheritance in family members of a breastfed infant who succumbed to fatal opioid intoxication and whose codeine-prescribed mother was a CYP2D6 UM, we constructed a pedigree. While the pedigree approach is helpful to aid diagnosis, identify other at risk family members, and simplify pharmacogenetic analysis, its clinical usefulness is dependent on an institutional framework which is not available in most centers at this time.

Keywords: CYP2D6, duplication, codeine, breastmilk, ultrarapid metabolism, pedigree.

INTRODUCTION

Cytochrome P450 2D6 (CYP2D6) is an enzyme involved in the oxidative metabolism of about 25% of medications on the market [1] and several endogenous substrates [2, 3]. Genotype to phenotype correlations are complicated by the highly polymorphic nature of CYP2D6 (M33388), with over 70 alleles identified [4] and by the presence of two highly homologous pseudogenes localized upstream of the CYP2D6 gene within the locus on chromosome 22q13 [5, 6]. The CYP2D6 ultrarapid metabolizer (UM) phenotype, which is of global importance [7], is predicted by duplications of functional CYP2D6 genes. The frequency of CYP2D6 gene duplication events varies depending on ethnicity (i.e. 2 – 6% of African Americans, 29% of Ethiopians, 10% of Saudi Arabsians, 1% of Swedish, 7% of Spanish and Portuguese) [8-12] and are believed to result from unequal crossover events during homologous recombination [13]. In addition, unequal segregation and extrachromosomal replication of acentric DNA may explain rare multiduplication events of up to 13 CYP2D6 copies in tandem [13].

In the case of the pro-drug codeine, CYP2D6 UM display on average 50% higher plasma concentrations of the pharmacologically active metabolite morphine than extensive metabolizers with only two functional gene copies, i.e. two fully functional alleles [14]. The gene-dose effect is such that increasing functional gene copies result in increased enzymatic activity and morphine production [14]. For codeine, this can cause serious toxicity even at therapeutic doses [15-17], for other drugs, the consequence may be therapeutic failure [18].

Following a fatal case of a breastfed infant whose mother was an ultrarapid metabolizer [17, 19], both the United States Food and Drug Administration [20] and Health Canada [21] have issued public health advisories highlighting a risk for opioid toxicity in breastfed infants whose codeine-prescribed mothers are CYP2D6 UM. With the advent of updated warning labels on codeine-containing medication for nursing mothers with the CYP2D6 UM phenotype [21], genetic counselors and other health care professionals may increasingly encounter demands for CYP2D6 genetic tests prior to codeine administration. In this report we describe the first analysis of CYP2D6 genotype in the extended family of the breastfed infant who died from opioid toxicity [17, 19].

METHODS

Genomic DNA was isolated with informed consent from blood and tissue (infant) using the QIAamp DNA Blood and Tissue Mini Kits (Qiagen, Valencia, CA, respectively).
CYP2D6 genotyping was conducted for the functional 
*40, reduced functional alleles *9, *10, *17, *29, *41, and 
the presence of *1xN, *2xN, *4xN gene duplications in the 
deceased infant and his parents. CYP2D6 copy number 
variation was quantified. Limited analysis was performed 
for the grandparents and aunts of the deceased baby (*2, *3, *4, 
of the deceased infant were genotyped only for the *2 and 
*2xN alleles. Allele designations were as defined by the 
CYP450 Allele Nomenclature Committee [4].

RESULTS AND DISCUSSION

The results illustrate an autosomal transmission of the 
functional CYP2D6*2Ax2, a single allele carrying two copies 
of the fully functional CYP2D6*2A variant, from the 
maternal grandmother to the mother, one of the aunts, and a 
subsequent sibling of the deceased infant (Fig. 1). The 
CYP2D6*2 allele has demonstrated a high susceptibility to 
multiduplication [8-10, 22] and comprises 72% of all 
duplications among Caucasians [23, 24]. All other family 
members were genotyped as extensive metabolizers, with 
two functional CYP2D6 alleles. The deceased infant, 
however, may have been physiologically incapable of 
metabolizing codeine and morphine which were invariably 
present in breast milk. CYP2D6 genotype to phenotype 
concordance has been observed from 2 weeks of postnatal 
age onwards [25, 26], but the overall clearance rate in 
newborns may be compromised until renal function and 
phase II drug metabolizing enzymes involved in morphine 
edition are fully matured [27]. Thus, at 12 days of age 
the infant’s cause of death was attributed to prolonged 
exposure to excessive morphine metabolite transmitted 
through the breast milk.

The CYP2D6 UM phenotype is not necessarily inherited 
in an autosomal dominant fashion. This is because gene 
amplification per se does not always translate into the UM 
phenotype. For one, the nature of the second allele has to be 
considered. But one also has to bear in mind that not all gene 
duplications are equal. For example, CYP2D6*4xN is a non-
functional allele and CYP2D6*10xN and CYP2D6*41xN 
constitute duplications of genes encoding enzymes of 
reduced function. The latter confer higher activity compared 
to their ‘single gene’ counterparts, but are likely not reaching 
the same level of ultrarapid activity conveyed by 
CYP2D6*1xN and *2xN (duplications of fully functional 
genes). Noteworthy, in Caucasians, the majority of gene 
duplications are fully functional (CYP2D6*1xN and *2xN), 
while almost half of all duplication events in African 
American populations are composed of non-functional genes 
(CYP2D6*4xN) [23]. Testing strategies which include 
determination of copy number variation are necessary to 
elucidate the relative increase in enzymatic activity. For 
CYP2D6, copy numbers between 2 and 13 alleles have been 
reported [8-10, 22].

CYP2D6 inheritance depends on the combination of 
maternal and paternal alleles in accordance with Mendel’s 
second law of independent assortment. This is exemplified 
by differential genotypes in the three sisters of the maternal 
line and also in their offsprings. Thus, siblings must be 
individually genotyped to determine the potential for risk of 
sedation and toxicity when taking codeine and/or 
breastfeeding their children. As CYP2D6 is subject to 
inhibition by a wide range of chemical substrates, clinical 
counseling must also include potential drug-drug interactions 
that can result in phenocopying of reduced or null genotypes. 
Evidently, in addition to maternal genotype, factors such as 
maternal codeine dose, duration, neonatal milk intake, and 
neonatal metabolic clearance capacity may also contribute to 
adverse drug reactions in breastfed infants of codeine- 
prescribed mothers [28, 29].

CYP2D6 also mediates the metabolism of other 
commonly used opioid analgesics- oxycodone, hydrocodone, 
and tramadol- into potent, pharmacologically active
metabolites. The relationship between CYP2D6 UM and opioid toxicity has been less studied in these analytics compared to codeine, although an adverse drug event had been reported [30]. Until more safety data is generated, it is advised that CYP2D6 UM breastfeeding mothers should also avoid oxycodone, hydrocodone, and tramadol. A recent systematic review reports that non-steroidal anti-inflammatory drugs (NSAIDs) may be an equipotent alternative to codeine-acetaminophen for the treatment of post-abdominal surgery pain [31].

Pedigree analysis for CYP2D6 is a useful clinical tool to help identify at risk family members, aid diagnosis, and help establish a pattern of inheritance [32]. The interpretation of CYP2D6 genotype into UM phenotype necessitates an understanding of the highly polymorphic nature of the CYP2D6 gene. This pharmaco genetic knowledge, alongside patient education and maternal and neonatal monitoring, can be used as preventative clinical tools to avoid opioid-related toxicity. Thus, educational and clinical methods must be developed to enable health care providers to provide needed counselling and genetic services in order to meet the growing shortage of professional genetic personnel [33]. As strategies on translating and incorporating new pharmaco genetic knowledge into clinical practice lag considerably behind rapid scientific advances, more studies are needed to address these shortcomings.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the family members and the genetic counselling team involved in this study as well as Dr. Ute I. Schwarz and Ms. Inna Y. Gong for their genotyping efforts. PM is supported by a postdoctoral fellowship from the Canadian Pharmacogenomics Network for Drug Safety.

REFERENCES

