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Cytochrome P450 2D6 Polymorphisms and Predicted Opioid Metabolism in African-American Children with Sickle Cell Disease

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Abstract

The opioid medications codeine and hydrocodone, commonly prescribed in sickle cell disease (SCD), require metabolic conversion by cytochrome P450 2D6 (CYP2D6) to morphine and hydromorphone, respectively, to exert their analgesic effects. The *CYP2D6* gene is highly polymorphic, with variant alleles that result in decreased, absent, or ultrarapid enzyme activity. Seventy-five children with SCD were tested for *CYP2D6* polymorphisms, and metabolic phenotypes were inferred from the genotypes. The most common variant alleles were *CYP2D6**2 (normal activity, 28.7%), *CYP2D6**17 (reduced activity, 17.3%), *CYP2D6**5 (gene deletion, 8.7%), and *CYP2D6**4 (absent function, 8.0%). Normal/extensive metabolizer (EM) genotypes were found in 28/75 (37.5%), intermediate metabolism (IM) in 33/75 (44.0%), poor metabolism (PM) in 4/75 (5.3%), ultrarapid metabolism (UM) in 3/75 (4.0%), indeterminate in 6/75 (8.0%). Allele frequencies did not vary significantly among different hemoglobin genotypes. Identification of variant *CYP2D6* genotypes may identify individuals with altered metabolism and therefore altered analgesic response to codeine and hydrocodone, thus providing a personalized medicine approach to treatment of pain in SCD. Further pharmacokinetic and pharmacodynamic studies are needed to define the relationship of *CYP2D6* and other gene polymorphisms to individual opioid effect in SCD.

Keywords

Sickle Cell Disease; Pharmacogenetics; Pain Medicine

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Disclosure

The authors have no conflicts of interest to disclose.

Introduction

Opioid analgesic medications are a mainstay of treatment for mild to moderate vaso-occlusive crisis (VOC) in sickle cell disease (SCD), and nearly all SCD patients will have exposure to these medications at some point during childhood. The commonly prescribed opioids codeine and hydrocodone are inactive prodrugs which require *in vivo* O-demethylation by the hepatic enzyme cytochrome P450 2D6 (CYP2D6) to the active analgesics morphine and hydromorphone, respectively [1–3]. Although CYP2D6 metabolism is a minor pathway of codeine metabolism, representing only 5 – 10% of codeine clearance, it is a required initial step for the opioid's analgesic effect [2]. Clinical response to opioid medications varies among individuals for numerous reasons, including drug bioavailability and distribution, genetic polymorphisms in metabolizing enzymes and opioid receptors, and the pharmacokinetics of drug clearance [4]. With personalized medicine, genetic information, such as *CYP2D6* polymorphisms, may be used to predict the metabolism of specific medications, thus providing information about drug efficacy for individual patients.

CYP2D6 is encoded by a highly polymorphic gene on chromosome 22 and has over 80 known variant alleles described to-date (listed at <http://www.cypalleles.ki.se/cyp2d6.htm>). The wild type *CYP2D6* allele is denoted as *1, with variant alleles noted as *2, *3, etc [5]. Combinations of single nucleotide polymorphisms (SNPs) may result in gene products with normal, decreased, or non-functional enzyme activity. *CYP2D6* genotypes can be categorized into phenotypic groups based on the variant enzymes' activity. Extensive metabolizers (EM) have normal enzyme activity; this includes individuals with 2 normal function alleles and some heterozygotes with normal and decreased activity alleles. Intermediate metabolizers (IM) have decreased enzyme activity; typically this is due to heterozygosity for a non-functional allele or homozygosity for two decreased activity alleles. Poor metabolizers (PM) have absent or little enzyme activity; this is due to homozygosity or compound heterozygosity for two non-functional alleles. Ultra-rapid metabolizers (UM) have greater than normal activity and are the result of duplications of active alleles [2,6]. The UM phenotype leads to rapid clearance of the substrate drug, thus providing minimal or brief therapeutic effect and/or abrupt drug toxicity [7–9].

The frequency of *CYP2D6* polymorphisms and phenotypes varies significantly among different racial and ethnic populations, and studies of *CYP2D6* polymorphisms within the U.S. sickle cell population to date have been limited to examining a small number of variant alleles. A study by Brousseau et al. of 73 SCD children presenting with VOC unrelieved by oral codeine found that 58% had at least one reduced or non-functional allele [10]. A genotyping study by Joly et al. showed reduced CYP2D6 metabolic activity in the majority of patients [11]; however to date, there are no studies of *CYP2D6* genotypes prevalence in the African-American SCD population. The aim of this study was to determine the frequency of *CYP2D6* alleles and genotypes in an unselected cohort of children with SCD by testing for the most common SNPs described in the U.S. and African-American populations.

Materials and Methods

Children ages 6 to 18 years with SCD of any genotype who presented to Children's Healthcare of Atlanta (CHOA) for outpatient care were offered study participation. Subjects were enrolled competitively over a 4 month period from March – July 2009 without selection or exclusion criteria other than subject or guardian refusal. This study was approved by the Institutional Review Boards (IRB) of Emory University and CHOA. Written, informed consent was obtained to test *CYP2D6* polymorphisms using previously

collected, discarded blood specimens. To eliminate the chance of sampling foreign DNA from recent blood transfusions, patients were excluded if they had received blood transfusion within the prior 48 hours.

CYP2D6 Genotyping and Phenotype Inference

DNA was extracted from whole blood specimens using the MagnaPureLC System (Roche Applied Science, Indianapolis, IN). Single multiplex polymerase chain reaction (PCR) was performed to identify the following 16 SNPs in *CYP2D6* using the xTag 2D6 (Luminex Corp., Austin, TX): 1548 C>G, 1661 G>C, 2850 C>T, 4180 G>C, 2549 delA, 100 C>G, 1846 G>A, 1707 delT, 2935 A>C, 1758 G>T, 2613 delAGA, 883 G>C, 124 G>A, 138 insT, 1023 C>T, 2877 G>A. Additionally, gene deletion (allele *5) and gene duplications were detected. The combination of these SNPs and mutations allowed for the identification of 2 active alleles (*1 or wild type and *2), 4 decreased activity alleles (*9, *10, *17, *41), and 10 non-functional alleles (*3, *4, *5, *6, *7, *8 or *14, *11, *12, *15). Because some SNPs are shared among numerous variant alleles, determination of the *CYP2D6* allele was based on combinations of several identified SNPs. If no SNPs were detected, the subject was assumed to be homozygous for the *1 wild type allele. The presence of multiple gene copies was tested; in instances of compound heterozygous genotypes with gene duplication, testing did not distinguish which allele had multiple gene copies.

For each genotype found in this study, the corresponding known enzymatic phenotype was assigned. The clinical phenotypes of enzyme activity for each *CYP2D6* allele, based on in vivo drug metabolism studies, have been previously described [6]. The presence of two functional alleles confers the EM phenotype, two non-functional alleles confer the PM phenotype, and two decreased activity alleles confer the IM phenotype. Individuals who are heterozygous for a functional allele and a decreased activity allele may have either the EM or IM phenotype. For example, the combination of a functional allele with *17 (reduced function allele) produces the IM phenotype, while the combination of a functional allele with the *10 or *41 reduced function alleles results in the EM phenotype [6,12,13]. In all cases possible, predicted phenotypes were assigned based on previously established drug metabolism studies for each genotype [6].

Statistical Analysis

Descriptive methods were used to present CYP2D6 allele frequencies and genotype frequencies. Allele frequencies were determined from the cohort's genotypes. For each individual, a genotype of 2 alleles was determined, thus the frequency of each allele was calculated using the denominator of 2-times the total number of subjects in the cohort. The frequency of each CYP2D6 phenotype among children of different hemoglobin genotypes was compared by Fisher's exact test.

Results

CYP2D6 allele testing was performed in 75 children with SCD: 51 (68.0%) HbSS, 15 (20.0%) HbSC, 4 (4.3%) HbS⁺ thalassemia (HbS⁺), 5 (6.7%) HbS⁰ thalassemia (HbS⁰). Racial and ethnic backgrounds were African-American in 73/75 and African in 2/75. The mean age was 12.5 years (range 6.3 – 18.8 years). There were 39 subjects on hydroxyurea (HU) and 5 subjects on chronic transfusions at the time of the study (2 subjects were receiving HU and transfusions concurrently).

CYP2D6 allele frequencies for the cohort are shown in Table I. The most prevalent alleles were the wild type allele *1 (30.7%) and the normal/increased activity allele *2 (28.7%). The frequency of decreased function alleles (*10, *17, *41) was 36/150 (24.0%), and the

frequency of non-functional alleles (*4, *5) was 25/150 (16.6%). Among the alleles that convey abnormal *CYP2D6* activity, *17 was the most prevalent (allele frequency 17.3%; genotype frequencies: 26.7% heterozygous, 4.0% homozygous subjects). Nine subjects had allele duplications: 3 with the UM predicted phenotype and 6 for whom phenotype was indeterminate due to the fact that these subjects were compound heterozygous for normal and reduced activity alleles. Alleles *3, *6, *7, *8, *9, *11, *12, and *15 which are rare in African-American populations (allele frequencies <1%), were not present in this cohort [2,6].

CYP2D6 genotype frequencies and predicted phenotypes are shown in Table II. The reduced activity phenotypes IM and PM represented a larger proportion of the study group than the normal activity EM phenotype. The most common phenotype was IM (33/75, 44.0%), followed by EM (28/75, 37.3%), PM (5/75, 6.7%), and UM (3/75, 4.0%). Because the genotype assay detected the presence of gene duplication but does not specify which allele is duplicated, phenotypes could not be inferred for 6 (8.0%) compound heterozygotes. Of these 6 subjects, 3 were heterozygous for a normal activity and a reduced/absent function allele (predicted phenotype of either UM or IM) and 3 were heterozygous for a non-functional allele and a reduced function allele (predicted phenotype of either PM or greater metabolic activity) [8]. Thus, the range of possible *CYP2D6* phenotypes in this SCD cohort is: 37.3 – 41.3% IM; 44.0 – 48.0% EM; 5.3 – 9.3% PM; 4.0 – 8.0% UM. Figure 1 compares the frequency of predicted *CYP2D6* phenotypes for each Hb genotype. There were no significant differences in either allele frequencies or predicted genotypes among subjects with HbSS, HbSC, HbS⁺ and HbS⁰ (data not shown).

Discussion

This study shows that a large proportion of SCD patients have variant *CYP2D6* genotypes that confer altered enzyme activity, thus potentially altering the normal pharmacokinetics and analgesic efficacy of the opioid medications codeine and hydrocodone. The *CYP2D6* allele frequencies in this cohort of SCD patients are similar to ranges reported in other U.S. African-American populations, with a slightly higher frequency of *CYP2D6* gene deletions [2,6,14,15].

Inadequate analgesic response to codeine or hydrocodone during sickle cell vaso-occlusive pain crises is a common reason for hospitalization. Many factors contribute to opioid analgesia, including the pharmacokinetics of drug bioavailability and clearance, drug metabolic activation, opioid receptor response, and transport of drug metabolites across the blood brain barrier. For codeine and hydrocodone, *CYP2D6* activity is the required first step in the pathway of opioid analgesic effect, converting the prodrug to morphine or hydromorphone, respectively. The high frequency of variant *CYP2D6* genotypes in this cohort of pediatric SCD patients suggests that altered *CYP2D6* activity is common in this population, possibly contributing to failure of analgesic response to codeine and hydrocodone in some patients. Thus *CYP2D6* genetic testing should be considered in patients with repeated episodes of failed outpatient pain management. Patients with genotypes that confer the PM and UM phenotypes will not respond to codeine or hydrocodone for pain relief, due to either the inability to convert these drugs into active analgesics (PM phenotype) or rapid drug activation and clearance, leading to potential rapid drug toxicity and ineffective analgesia (UM phenotype) [2]. Patients with the IM phenotype have some ability to produce active metabolites from codeine and hydrocodone; however these patients may not be able to achieve adequate analgesia with standard dosing and may require higher doses for therapeutic effect. Opioid medications that do not require enzymatic activation, such as morphine or hydromorphone may produce better analgesia in these patients.

CYP2D6 genotype is only one factor that affects opioid metabolic phenotype. *CYP2D6* is involved in the metabolism of approximately 25% of all medications [16], and its activity may be inhibited or induced by many common medications, such as H1 histamine receptor antagonists, selective serotonin release inhibitors, and methadone, leading to abnormal metabolism of codeine and hydrocodone [17,18]. Following enzymatic activation by *CYP2D6*, several other factors affect morphine and hydromorphone's analgesic effects. Darbari et al. demonstrated that morphine clearance is significantly higher in SCD as compared to non-SCD individuals, and may be related to increased hepatic metabolism and increased renal elimination that are unique to SCD [19]. Thus, SCD patients may require higher and more frequent opioid doses to maintain adequate concentrations for analgesia, independent of *CYP2D6* genotype. Additionally, variability in other genes that regulate opioid pharmacokinetics and pharmacodynamics, such as UDP-glucuronosyltransferase (responsible for morphine metabolism), the μ 3bc opioid receptor, and blood-brain-barrier transporter proteins, may decrease opioid efficacy or potentially promote opioid addiction [3,4,20]. Given the numerous confounding variables that affect both *CYP2D6* metabolic phenotype and opioid efficacy, further studies examining the associations of genetic variation in *CYP2D6* and other genes, codeine pharmacokinetics, and patient-reported analgesic effects are necessary.

A limitation of this study was the inability to identify less common *CYP2D6* alleles. Although the array of SNPs tested in this study allowed for the identification of 16 of the most common variant alleles, other less common alleles were not detectable by the study assay. Subjects who did not have one of the 16 tested SNPs were assumed to have the **1* wild type allele, thus rare SNPs and alleles may have been missed inadvertently. Discordance between *CYP2D6* genotype and phenotype has been observed in African populations, and may be due to unrecognized polymorphisms [15,21–23]. Our study also was limited by the ability to accurately determine the genotypes of a few individuals with gene duplications. Because we assayed for gene duplications by identifying *CYP2D6* gene sequences shared among different alleles, for individuals who are compound heterozygotes and have gene duplication, it was not possible to determine which variant allele is over-expressed by the methods used in this study.

In summary, pharmacologic pain management in SCD depends on numerous factors, including drug pharmacokinetics, pharmacogenetics of metabolizing enzymes including *CYP2D6*, and allelic variation in other genes involved in opioid efficacy, such as the μ opioid receptor. Because there is a high frequency of variant *CYP2D6* metabolizers in the African-American SCD population, clinicians should be aware that genetic variation in the *CYP2D6* gene may contribute to poor analgesic responses to common pain medications prescribed for outpatient SCD pain management. With personalized medicine, genetic testing allows clinicians to predict response to medications and customize individual treatments based on genetic polymorphisms. Larger studies of *CYP2D6* genotypes, codeine and hydrocodone pharmacokinetics, and pharmacodynamic measurements of opioid efficacy are needed to further define the extent to which *CYP2D6* phenotype contributes to failed outpatient management of pain in the SCD population.

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Figure 1. CYP2D6 Predicted Phenotypes in each sickle cell genotype

CYP2D6 predicted phenotypes were not significantly different among different sickle cell hemoglobin genotypes. Predicted phenotypes for HbSS were: 19/51 (37.3%) EM, 23/51 (45.1%) IM, 3/51 (5.9%) PM, 2/51 (3.9%) UM, and 4/51 (7.8%) unknown. Phenotypes for HbSC were: 3/15 (20.0%) EM, 8/15 (53.3%) IM, 2/15 (13.3%) PM, 1/15 (6.7%) UM, and 1/15 (6.7%) unknown. There were few subjects with HbS⁰ (n=5) or HbS⁺ (n=4) in this cohort. EM = extensive metabolizer, IM = intermediate metabolizer, PM = poor metabolizer, UM = ultra-rapid metabolizer.

CYP2D6 allele frequencies in 75 children with SCD. For each subject, both *CYP2D6* alleles were identified by SNP testing, thus determining the individuals' genotypes. The allele frequency represents the pool of 150 identified alleles among the 75 subjects.

Table 1

Allele	Genetic Alteration	Enzyme Activity	Heterozygous Subjects (%)	Homozygous Subjects (%)	Allele Frequency (%)
*1	Wild type	Normal	34/75 (45.3)	6/75 (8.0)	46/150 (30.7)
*2	Multiple SNPs	High/normal	35/75 (46.7)	4/75 (5.3)	43/150 (28.7)
*3	Frameshift	None	0	0	0
*4	Splicing defect	None	12/75 (16.0)	0	12/150 (8.0)
*5	Gene deletion	None	11/75 (14.7)	1/75 (2.0)	13/150 (8.7)
*6	Frameshift	None	0	0	0
*7	Missense mutation	None	0	0	0
*8/14	Nonsense mutation	None	0	0	0
*9	Frameshift	Decreased	0	0	0
*10	Multiple SNPs	Decreased	4/75 (5.3)	0	4/150 (2.7)
*11	Splicing defect	None	0	0	0
*12	Missense mutation	None	0	0	0
*15	Frameshift	None	0	0	0
*17	Multiple SNPs	Decreased	20/75 (26.7)	3/75 (4.0)	26/150 (17.3)
*41	Splicing defect	Decreased	2/75 (2.7)	2/75 (2.7)	6/150 (4.0)

Table II*CYP2D6* genotype frequencies in 75 children with SCD

Genotype	Frequency (%)
Extensive Metabolizers	28/75 (37.3)
*1/*1	5 (6.7)
*1/*2	15 (20.0)
*1/*10	1 (1.3)
*2/*2	4 (5.3)
*2/*10	1 (1.3)
*2/*41	2 (2.7)
Intermediate Metabolizers	33/75 (44.0)
*1/*4	2 (2.7)
*1/*5	6 (8.0)
*1/*17	7 (9.3)
*2/*4	3 (4.0)
*2/*5	2 (2.7)
*2/*17	8 (10.7)
*17/*17	3 (4.0)
*41/*41	2 (2.7)
Poor Metabolizers	5/75 (6.7)
*5/*5	1 (1.3)
*4/*5	2 (2.7)
*4/*17	1 (1.3)
*5/*17	1 (1.3)
Ultra-rapid Metabolizers	3/75 (4.0)
*1/*1 + DUP	1 (1.3)
*1/*2 + DUP	2 (2.7)
Indeterminate	6/75 (8.0)
*1/*10 + DUP	1 (1.3)
*2/*4 + DUP	1 (1.3)
*2/*10 + DUP	1 (1.3)
*4/*17 + DUP	3 (4.0)