Effects of *CYP2B6* allelic variants, infection status, liver fibrosis and steatosis on methadone pharmacokinetics

Andrew H. Talal, MD, MPH[1]; Yuxin Ding[2]; Charles Venuto, PharmD[3]; Lindsay Chakan, PhD[1]; Anthony McLeod, BS[4]; Arpan Dharia, MD[1]; Gene D. Morse, Pharm D[5]; Lawrence S. Brown, MD, MPH[4]; Marianthi Markatou, PhD[2]; Evan Kharasch, MD, PhD[6]

[1]Division of Gastroenterology, Hepatology and Nutrition, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY; [2]Department of Biostatistics, School of Public Health and Health Professions, University at Buffalo, Buffalo, NY; [3] University of Rochester, Rochester, NY; [4]START Treatment & Recovery Centers, Brooklyn, NY; [5]NYS Center of Excellence in Bioinformatics and Life Sciences University at Buffalo; [6]Duke University Medical Center, Durham, NC

Abstract

Background

Methadone is highly effective for treatment of opioid use disorder (OUD) and pain management. However, the narrow therapeutic index and inter-individual variability in disposition create dosing challenges. While overdose can lead to toxicity and death, sub-therapeutic doses can potentiate withdrawal. Recent data establish that CYP2B6 is the enzyme responsible for methadone metabolism to 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) instead of CYP3A4. *CYP2B6* alleles encode variant enzymes with loss-of-function (LOF) (*CYP2B6*6*, *CYP2B6*16*, *CYP2B6*18*) and gain-of-function (*CYP2B6*4*) compared to wild-type (*CYP2B6*1*). Methadone metabolism by the variant gene product CYP2B6.6 is less than, while CYP2B6.4 is greater than, that by CYP2B6.1. The frequency of *CYP2B6* alleles in a population consisting largely of African-Americans (AA), many of whom are also infected with HIV and/or hepatitis C virus (HCV), and influence on methadone disposition, has not been evaluated.

Description of methods

Pre-dose (trough) plasma was collected from 96 adults on stable daily, oral methadone for OUD. We measured (R)- and (S)-methadone and (R)- and (S)-EDDP concentrations as well as methadone metabolism-(logarithm of (R) and (S)-EDDP/methadone concentration ratio). We performed transient elastography to assess hepatic fibrosis and steatosis, and assessed the *CYP2B6* alleles principally responsible for methadone metabolism. We utilized a multivariate linear mixed effects model to analyze the effects of multiple predictors (sex, body mass index (BMI), *CYP2B6* genotype, concomitant medication) on plasma methadone metabolism. Significance was set at $p<0.05$.

Results

Participants were largely male (58%), minority (61% AA, 28% Caucasian) and non-Hispanic (68%). 41% were HCV mono-infected, 41% were uninfected, and 18% were HIV/HCV co-infected. Modeling results reveal that female has a significant effect (p=0.035) on (R)-methadone metabolism but has borderline effect on (S)-methadone metabolism (p=0.071). LOF alleles are highly significant on (S)-methadone metabolism (p=0.012) and have borderline effect on (R)-methadone metabolism (p=0.066). BMI also has borderline significant effect (p=0.084) on (R)-

methadone metabolism. Methadone metabolism appears to be decreased in males and individuals with LOF alleles. Liver stiffness has no significant effect on methadone metabolism.

Conclusions

In the age of precision medicine, genetic analysis is essential to delivering individualized treatments. It is crucial to include minority populations in genetic studies as some alleles are race specific. Our results suggest that sex and *CYP2B6* genotype should be incorporated into multivariate models, along with other predictors (e.g. BMI), to create dosing algorithms. The development of a methadone dosing algorithm should facilitate methadone delivery as well as improve patient satisfaction with methadone prescription and prevent overdose.

	HCV-mono (n= 39)	**HIV/HCV (n=18)**	**Uninfected (n=39)**	**Total (n=96)**
Sex				
Male	28 (72%)	11 (61%)	17(44%)	56 (58%)
Female	11 (28%)	7 (39%)	22 (56%)	40 (42%)
Race				
Black or African American	22 (56%)	9 (50%)	28 (72%)	59 (61%)
Caucasian	13 (33%)	8 (44%)	6 (15%)	27 (28%)
Others	4 (11%)	1 (6%)	5 (13%)	10 (11%)
Ethnicity				
Non-Hispanic or Latino	24 (62%)	10 (56%)	31 (79%)	65 (68%)
Hispanic or Latino	15 (38%)	8 (44%)	8 (21%)	31 (32%)
Age, years (Median, IQR)	58 (13)	60.5 (13)	53 (11)	56 (14)
BMI, kg/m^2 (Median, IQR)	26 (7)	23 (3)	29 (9)	25 (8)

Abbreviation: IQR-interquartile range