Understanding How HIV and Hepatitis C Virus (HCV) Infection Affects CYP2B6 Enzymatic Activity and Methadone Pharmacokinetics

Andrew H. Talal, Charles S. Venuto, Yuxin Ding, Arpan Dharia, Clewet Sylvester, Heidi Nieves-McGrath, Anthony Mcleod, Gene D. Morse, Marianthi Markatou, Lawrence S. Brown, Evan D. Kharasch

1Department of Medicine, University at Buffalo; 2Department of Neurology, University of Rochester; 3START Treatment & Recovery Centers; 4Anesthesiology, Duke University School of Medicine

Background

- Methadone is one of three medications approved for the treatment of opioid use disorder (OUD).
- Its 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.
- We seek to develop safe, effective methadone dosing strategies by elucidating the associations between CYP2B6 genetic polymorphisms and methadone disposition in HIV and HCV patients.

Rationale

- CYP2B6 is a polymorphic, methadone metabolic enzyme with 38 variant alleles identified through single-nucleotide polymorphisms (SNP).
- Several loss-of-function alleles (CYP2B6*5, CYP2B6*6, CYP2B6*7, CYP2B6*16, CYP2B6*18) express low enzymatic activity and catalyze less methadone N-demethylation to metabolite 2-ethylidene-1,5-dimethyl-3-diphenylpyrrolidine (EDDP) compared to wild-type (CYP2B6*1).

Hypothesis

- We hypothesize that HIV and HCV infection affects CYP2B6 enzymatic activity.

Study Design and Entry Criteria

- We enrolled adult patients receiving once-daily methadone for opioid replacement therapy (ORT) cross-sectionally.
- HIV and HCV infection status assessed within one year.
- Patients required stable methadone dose for at least 14 days with ≥80% adherence and at least 90 days on ORT.
- Body mass index <40 kg/m² and no active HCV treatment.

Study Assessments

- Ultrasound-based vibration controlled transient elastography (FibroScan®) assessed hepatic stiffness (elasticity) (i.e. fibrosis) and controlled attenuation parameter (CAP) (i.e. steatosis).
- Demographic data included height, weight, age, gender, race, ethnicity, methadone dose, nicotine and alcohol consumption, substance use, and concomitant medications.
- Laboratory data included liver function, hematology, virologic status, and blood chemistry obtained from medical records.
- (R)- and (S)-methadone and (R)- and (S)-EDDP concentrations were assessed on plasma samples (~24 hours post-dose).
- Genomic DNA was extracted from whole blood and genotyped for the CYP2B6 516G>T (rs3749274), 785A>G (rs2279343), 983T>C (rs2839949) and 1459C>T (rs3211371) SNP.

Baseline Characteristics

- Most participants are male, African American, non-Hispanic.
- BMI was highest in uninfected and lowest in HIV/HCV co-infected.
- Liver stiffness was highest in HIV/HCV co-infected, and lowest in uninfected.
- Steatosis was highest in uninfected and lowest in HIV/HCV co-infected.
- Dose-normalized (R)-methadone did not significantly by infection status.
- *1/1 and *1/6 were the two most frequent CYP2B6 alleles.

CYP Allele Affect on Methadone PK

- CYP2B6*6/16 appears to be a novel SNP responsible for methadone metabolism.
- HCV infection also appears to affect CYP2B6*6/16 methadone metabolism.
- HIV/HCV co-infection also appears to affect CYP2B6*6/16 and*6/6 methadone metabolism (data not shown).

Conclusions

- We noted an inverse relationship between liver stiffness and steatosis based upon infection status.
- HIV and HCV infection status appear to influence methadone metabolism by different alleles.
- CYP2B6*6/16 may be a novel SNP.
- Further investigation is needed to discern if these findings persist in larger populations and to elucidate potential mechanisms.