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

Andrew H. Talal¹, Charles S. Venuto², Yuxin Ding¹, Arpan Dharia¹, Clewert Sylvester³, Heidi Nieves-McGrath¹, Anthony Mcleod³, Gene D. Morse¹, Marianthi Markatou¹, Lawrence S. Brown³, Evan D. Kharasch⁴

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 essential medications approved for treatment of opioid use disorder. However, it’s 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. We initially sought to elucidate the association between CYP2B6 genetic polymorphisms and methadone disposition in HIV and HCV patients.

Rationale/Significance: CYP2B6 is a polymorphic, methadone metabolic enzyme with 38 variant alleles identified through single-nucleotide polymorphisms. Several loss-of-function alleles (CYP2B6*5, CYP2B6*6, CYP2B6*7, CYP2B6*16, CYP2B6*18) express low activity and CYP2B6.6 and CYP2B6.9 catalyze less methadone N-demethylation to metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) compared to wild-type (CYP2B6.1*1).

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

Results: Pre-dose (trough) plasma was collected from 98 adults on daily, oral methadone for measurement of (R&S)-methadone and (R&S)-EDDP concentrations. Participants were minority (61% African-American, 28% Caucasian) and non-Hispanic (68%). Exploratory data analysis revealed that mean (R&S)-methadone concentrations appear to be similar between wild-type and loss-of-function alleles. Analysis by infection status (HIV/HCV co-infected, HCV mono-infected, uninfected) revealed that CYP2B6*7 activity was particularly diminished in co-infected participants as indicated by higher (R&S)-methadone concentrations compared to wild-type and lower EDDP/(R&S)-methadone ratios compared to mono-infected participants. Co-infected CYP2B6*6 homozygotes (*6/*6) also revealed numerically greater (R&S)-methadone concentrations compared to CYP2B6*6 carriers (*1/*6) and wild-type (*1/*1).

Discussion: Co-infection particularly affects CYP2B6*7 and *6/*6 enzymatic activity. Results suggest that infection status may affect CYP2B6 enzymatic activity with regard to methadone pharmacokinetics.