Stereoselective Population Pharmacokinetics and Pharmacogenomics of Intravenous Methadone

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Background/Introduction: Methadone is chiral and generally used clinically as a racemic mixture of R- and S- enantiomers. R-methadone mu-receptor binding affinity and analgesic potency are 30- to 50-fold greater than S-methadone, thus R-methadone is responsible for the majority of racemic methadone analgesia. There is an unmet need for a) a comprehensive population pharmacokinetic model of methadone and its major inactive metabolite 2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) derived from dense, early sampling times extending to 4 days after a single dose, b) the influence of genetic CYP variants on disposition, and c) a more comprehensive evaluation of chiral effects on the disposition of methadone and EDDP.

Methods: R- and S-methadone and EDDP plasma concentrations were measured in 1214 blood samples obtained over 4 days from 64 healthy subjects, following a single 6 mg IV dose of racemic methadone. 5 *CYP2B6* genotypes and 7 *CYP2C19* genotypes were determined for each subject. Parameters for a 3-compartment population pharmacokinetic model were estimated using Phoenix NLME 8.4.3. Proportional links (S:R) between the 3-compartment models of S- and R-methadone were evaluated for volume, intercompartmental clearance and elimination clearance estimates. Demographic and genotype data were evaluated with a stepwise covariate analysis. Individual Bayesian estimates of the final methadone model were carried forward in a stepwise manner to model the population pharmacokinetics of EDDP.

Results: Figure 1 demonstrates the differential concentration versus time relationships for R- and S-methadone. Central, rapidly, and slowly equilibrating volumes of distribution of a 3-compartment model for S-methadone were estimated to be 46.1±7.0, 172.4±9.7, and 181.9±11.5 L, respectively; intercompartmental clearances to rapid and slow equilibrating peripheral compartments were11.0±2.0 and 0.44±0.06 L/min, respectively; and elimination clearance was0.078±0.01 L/min. Introduction of estimated proportionality constants (S:R) for distribution volumes (0.60±0.01), intercompartmental clearances (0.77±0.02) and elimination clearance (0.87±0.02) significantly reduced the OFV (-2LL) of the population pharmacokinetic model. Sex and *CYP2B6* genotype were significant covariates for elimination clearance and body weight was a significant covariate for the slow volume of distribution.

Conclusion: 3-compartment pharmacokinetics of R- and S-methadone differ and can be well described by proportionality constants applied separately to distribution volumes, intercompartmental clearances, and elimination clearance. These systematic differences among parameter estimates suggest the influence of chirality on protein binding and metabolism as well as the presence of significant rbc:plasma partitioning for methadone. *CYP2B6* genotype, but not that of *CYP2C19*, explains some of the interindividual variability in elimination clearance.

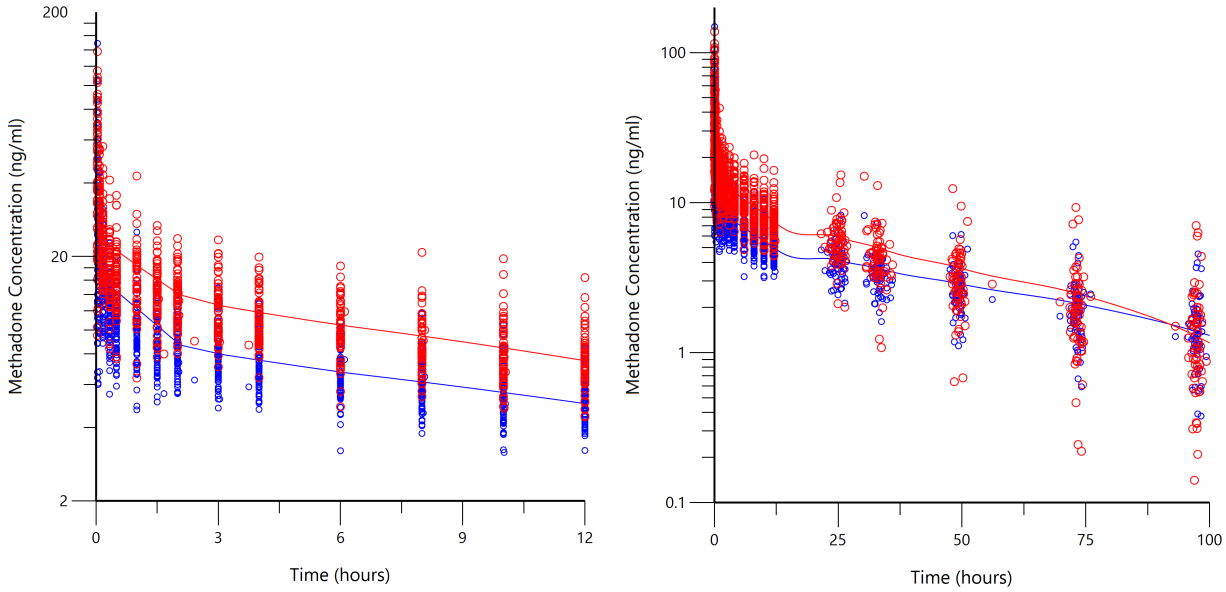

Figure 1. Observed plasma R-methadone (blue circles) and S-methadone (red circles) versus time for all 64 subjects. The left graph is for the first 0-12 hour, which highlights stereoselective differenecs in distribution and the right graph is for the full 0-96 hours. Red and blue solid lines represent the loess central tendencies.