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Prevention

QTc PROLONGATION CORRELATES WITH PLASMA ETHYLIDENE-1,5-DIMETHYL-3,3-DIPHENYLPYRROLIDENE (EDDP) AMONG SUBJECTS INITIATING METHADONE MAINTENANCE THERAPY

Moderated Poster Contributions

Poster Sessions, Expo North

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Background: Methadone-associated sudden death is a leading public health issue. High plasma methadone concentration (PMC) and QTc interval prolongation increase risk for sudden death. We examined clinical, genetic and pharmacokinetic variables and methadone dose for associations with plasma methadone concentrations and QTc prolongation.

Methods: Consenting participants (n=31) initiating methadone maintenance therapy were enrolled in the MEMORIES Trial (ClinicalTrials.gov NCT01191242). Peak (4 hr post-oral dose) and trough (24 hr) plasma samples obtained on days 1, 7 and 21 were analyzed for methadone and EDDP (the principal methadone metabolite) by liquid chromatographic tandem mass spectrometry. Pre-treatment and d21 rate-corrected QT interval (QTc) was measured by ECG.

Results: PMC was associated with dose and body mass index, although 60.4% of PMC variability was unexplained by dose. Variants in ABCB1, CYP3A4 and CYP2B6 genes were not predictive of PMC; however, stereo-selectivity of CYP2B6 was reduced by the variant rs3745274. Baseline QTc did not predict day (d) 21 QTc ($r^2=0.056$, $p=0.25$); however d21 trough plasma EDDP was highly correlated with QTc ($r^2=0.386$, $p=0.001$). For subjects with d21 QTc ≥ 447 msec (n=6), d21 trough EDDP was 43.8 ± 15.4 ng/mL vs 22.9 ± 10.7 ng/mL for QTc < 447 msec, $p=0.004$). Findings were similar on d 8 ($r^2=0.197$, $p=0.026$; 104.4 ± 36.7 ng/mL and 70.2 ± 26.1 ng/mL for QTc \geq and < 447 msec, respectively, $p<0.02$). Trough EDDP ≥ 25 ng/mL predicted day 21 QTc ≥ 447 msec, with sensitivity of 100% and specificity of 78.9%.

Conclusions: Individual response to oral methadone is highly variable and incompletely explained by dose or currently known clinical and genetic variables. Variables, presently unknown, may account for the remainder of inter-individual variability. Methadone-increased QTc interval directly correlated with plasma trough level EDDP as early as d8 and, at d21, identified with 100% sensitivity those with QTc ≥ 447 msec. The use of EDDP appears promising as a risk marker for QTc prolongation and deserves further study.