K50 Disposition of Buprenorphine and Norbuprenorphine in Human Meconium

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This presentation will provide attendees with the first data on concentrations, ratios and extent of glucuronidation of buprenorphine and norbuprenorphine in meconium following controlled buprenorphine administration to a cohort of pregnant women.

This presentation will impact the forensic community by providing the first data on buprenorphine and norbuprenorphine excretion in meconium following controlled drug administration to a cohort of pregnant women. These data provide valuable information on buprenorphine and norbuprenorphine concentrations and the extent to which these analytes may be conjugated in meconium. Additionally, these data allow for correlations to be examined between maternal dose and meconium concentrations and between meconium concentrations and neonatal outcomes, providing critical information for clinicians.

Buprenorphine is currently being investigated in the United States as a pharmacotherapy for treating opioid dependence in pregnant women. The disposition of buprenorphine and norbuprenorphine was evaluated in meconium from infants born to nine women participating in a study approved by the Johns Hopkins Bayview Medical Center and National Institute on Drug Abuse Institutional Review Boards comparing methadone and buprenorphine for the treatment of opioid dependence during gestation.

Women were treated with 14-24 mg/day buprenorphine for the last 12-22 weeks of pregnancy. Meconium specimens (N=10, one set of twins) were analyzed using the first validated liquid chromatography-tandem mass spectrometry with atmospheric pressure chemical ionization method. Two aliquots (0.25 ± 0.1 g) of each specimen were analyzed, one with and one without enzyme hydrolysis. Hydrolysis efficiency was evaluated in each analytical run using hydrolysis controls that quantified within 7.2% of target. Analyte recovery from meconium was at least 77% with buffer extraction followed by solid phase extraction. The assay was linear from the method's limit of quantification of 20 ng/g to 2000 ng/g for buprenorphine and norbuprenorphine. Accuracy was >86% and precision >84% with no interference from 69 tested licit and illicit drugs and metabolites.

Total buprenorphine concentrations ranged from 24-297 ng/g with a mean (±SE) of 131 ± 27 ng/g and a median concentration of 110 ng/g. Free buprenorphine ranged from 24-240 ng/g (mean = 93 ± 23; median = 60 ng/g). One specimen, which contained 24 ng/g total buprenorphine, had free buprenorphine concentrations below the method's limit of quantification. The percent free buprenorphine was 35-82%, with an average of 64 ± 6%, indicating inter-subject variation in glucuronide conjugation. Matched-pair t-test of total and free analysis indicated a statistically significant higher concentration of total buprenorphine than free (mean difference = 49 ± 10 ng/g, n=9 pairs, t=4.788, 8df, p=0.001). Specimens contained higher con- centrations of total and free norbuprenorphine, 324-1880 (mean = 754 ± 136 ng/g; median = 660 ng/g) and 331-1229 ng/g (mean = 610 ± 88 ng/g; median= 501 ng/g), respectively. Four specimens had >99% free norbuprenorphine. Three of these actually had lower total than free drug concentrations, but results were within ± 20%, the imprecision of the analysis. Another possibility could be the difficulty in completely homogenizing meconium. The remaining specimens (N=6) ranged from 53-89% free norbuprenorphine (mean 71 ± 6%). There was no statistically significant difference between the concentration of total norbuprenorphine and the concentration of free drug (mean difference = 143 ± 78 ng/g, t=1.840, 9df, p=0.099).

The free buprenorphine to free norbuprenorphine ratio was 0.14 ± 0.02 ng/g (range: 0.07-0.20 ng/g; median = 0.14) and the total buprenorphine to total norbuprenorphine ratio was 0.18 ± 0.03 ng/g (range: 0.05-0.33 ng/g; median = 0.16.). There is no statistically significant difference between these two ratios (p=0.37).

These findings impact the forensic community by providing the first data on buprenorphine and norbuprenorphine excretion in meconium following controlled drug administration to a cohort of pregnant women. These data provide valuable information on buprenorphine and norbuprenorphine concentrations and the extent to which these analytes may be conjugated in meconium. Additionally, these data allow for correlations to be examined between maternal dose and meconium concentrations and between meconium concentrations and neonatal outcomes, providing critical information for clinicians.

Buprenorphine, Meconium, Pregnancy

 ** Presenting Author*