K65 Buprenorphine and Metabolites in Paired Breast Milk and Maternal and Infant Plasma Specimens

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After attending this presentation, attendees will be able to describe the transfer of Buprenorphine (BUP) from maternal sublingual buprenorphine therapy to infants via breastfeeding.

This presentation will impact the forensic science community by strengthening evidence that BUP should be an approved therapy for medication-assisted, opioid-dependent women who breastfeed and abstain from illicit drug use.

Opioid abuse during pregnancy is a growing public health concern and is associated with fetal growth restriction, placental abruption, fetal death, and Neonatal Abstinence Syndrome (NAS). Lactation is known to reduce NAS severity, and women receiving methadone therapy are encouraged to breastfeed if they do not use illicit drugs. Recently, the Academy of Breastfeeding Medicine revised their protocol to also recommend BUP-treated mothers to breastfeed, despite a lack of conclusive infant safety data. This study sought to quantify BUP and its active phase I and phase II metabolites in breast milk and maternal and infant plasma of BUP-maintained women and their infants.

Ten opioid-dependent, BUP-maintained women (2mg-22mg/day, sublingually) provided paired breast milk and plasma specimens (2h-2.5h after daily sublingual dose) on days 2, 3, 4, 14, and 30 post-delivery, and nine infants provided plasma specimens on day 14, as part of this Johns Hopkins University School of Medicine Institutional Review board-approved study. Plasma and breastmilk samples (100µL) were quantified for BUP, Norbuprenorphine (NBUP), BUP-Glucuronide (BUP-Gluc), and NBUP-Gluc by a previously validated liquid chromatography/tandem mass spectrometry method. Briefly, samples were fortified with deuterated internal standards and proteins precipitated with acetonitrile. Supernatants were diluted with phosphoric acid and extracted on solid phase polymeric, strong cation exchange cartridges. Linear ranges were 0.1-20 (BUP, BUP-Gluc), 0.25-50 (NBUP-Gluc), and 2-100 (NBUP) µg/L. Bias and imprecision were <±16%. Non-parametric correlation coefficients (Spearman) assessed correlations between BUP dose and concentrations with a $p < 0.05$ significance threshold.

Women were 26.1 ± 4.7 years old. Ninety percent of women were cigarette smokers and only three exclusively breastfed their infants. Infants were born at term with appropriate birth weights; only one infant required treatment for mild NAS for 12 days. BUP (median (range)) was detected in all breast milk (2.4 (0.2-20.8) µg/L) and plasma (1.9 (0.4-7.0) µg/L) samples on all days from all mothers. BUP-Gluc, NBUP, and NBUP-Gluc were detected > Limit Of Quantification (LOQ) in 16/44 (0.1-0.3µg/L), 18/44 (1.0-4.1µg/L), and 36/44 (0.3-5.1µg/L) breast milk samples, respectively. BUP-Gluc, NBUP, and NBUP-Gluc were detected > LOQ in 44/46 (0.1-9.3µg/L), 27/46 (2.1-12.4µg/L), and 46/46 (1.2-42.2µg/L) maternal plasma samples, respectively. Ratios of median BUP in breast milk to median BUP in maternal plasma were 0.7 (day 4)-2.0 (day 14). Statistically significant correlations (rho) between maternal dose and maternal plasma BUP concentrations were 0.67 (day 14)-0.85 (day 2). Statistically significant correlations between maternal dose and breast milk BUP concentrations were 0.64 (day 3)-0.88 (day 4).

BUP was detected in 4/9 infant plasma samples at 0.2µg/L, 0.7µg/L, 1.0µg/L, and 2.9µg/L. Only one exclusively breastfed infant had detectable BUP (0.7µg/L). No metabolites were detected > LOQ in any infant plasma sample. Using a 600mL/day breast milk approximation for an exclusively breastfeeding infant at two weeks of age and a 4.8µg/L median BUP breast milk concentration, a maximum relative infant dose of 2.9µg/day of BUP is possible and well below BUP doses tested to treat NAS (15.9µg/kg/day).

BUP was detected in less than half of the infants and at low concentrations. Metabolites associated with sedation were not detected in infant plasma. The significant correlations between maternal BUP dose and maternal plasma and breast milk concentrations in this study were not observed in previous methadone studies and could be due to BUP's higher lipophilicity. Although increasing BUP concentrations in breast milk warrant further study, data from this small cohort contribute to the recommendation for breastfeeding in BUP-maintained women.