K49 Methadone Disposition in Human Breastmilk and Plasma in the Immediate Perinatal Period

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After attending this presentation, attendees will learn about the methadone content in human breastmilk in the immediate postnatal period, its relationship to maternal methadone dose and maternal and infant plasma concentrations, and the variability in breastmilk methadone concentrations in fore- and hindmilk.

This presentation will impact the forensic science community by demonstrating how the findings that maternal methadone dose was unrelated to plasma and breast milk methadone concentrations and that infant methadone exposure from breastmilk was low, support the recommendation that methadone-maintained women be permitted to breastfeed their infants if appropriate and desired.

Methadone maintenance is the only recognized pharmacologic treatment for opiate dependency during pregnancy in the U.S. It is well established that breastfeeding is the optimal way to nourish an infant. Breastmilk confers known advantages to mother and infant and could be beneficial for methadone-exposed infants at risk for morbidity in the perinatal period. However, lactation among methadone-maintained women is frequently challenged due to lack of knowledge about this practice. 2,257 women enrolled in a comprehensive substance abuse treatment program for pregnant and post-partum drug dependent women were screened for participation. Any woman considered intoxicated or having a positive urine test was excluded from further participation. Eight methadone-maintained (dose range 50–105 mg/day), lactating women provided blood and breastmilk specimens on days 1, 2, 3, 4, 14, and 30 after delivery at the times of trough (just before methadone dose) and peak (3 hours after dosing) maternal methadone levels. Paired specimens of foremilk and hindmilk were obtained at each sampling time. Eight matched formula-feeding subjects had blood drawn the same days. Infant blood for both groups was obtained on day 14 concurrent with a heelstick for routine pediatric care. All infants underwent neurobehavioral testing using the NICU Network Neurobehavioral Scale on days 3, 14, and 30.

Breast milk was collected in polypropylene storage vials and stored at -20°C until time of analysis. Specimens were analyzed using a validated liquid chromatography atmospheric pressure chemical ionization tandem mass spectrometry method. Breastmilk, 0.5 mL was analyzed following protein precipitation and solid phase extraction. The limit of quantification (LOQ) was 10 ng/mL with a linear dynamic range of 10 – 500 ng/mL. Extraction efficiency was greater than 97% with inter- and intra-day imprecision < 20%. Blood was collected in heparinized tubes, centrifuged, and plasma separated and stored at -20°C until time of analysis. Plasma specimens were analyzed by gas chromatography mass spectrometry fol- lowing solid phase extraction. LOQ for methadone was 5.0 ng/mL and range of linearity was 5 – 2000 ng/mL. Intra- and inter-day imprecision was <20%.

Repeated measures linear regression was used to determine whether there was a significant change over time days 1 through 30 in breastmilk methadone concentrations for each sampling time (trough prefeed, trough postfeed, peak prefeed, peak postfeed) and whether there was an effect of breastfeeding (yes/no), time (day 3, 14, 30) or breastfeeding by time inter- action for neurobehavioral outcomes. Statistical significance was set at $P < 0.05$ for all analyses.

Methadone doses among subjects and controls varied little in the post- partum period and were (median (range): 70 mg (50 – 105 mg) at delivery, and days 14 and 30. Concentrations of methadone in breastmilk were low (range 21.0–462.0 ng/mL) and not related to maternal dose. There was a significant increase in methadone concentrations in breastmilk over time, and concentrations increased from pre- to postfeed in all cases aside from the first collection (colostrum). There were no significant effects of breastfeeding on neurobehavioral outcomes. Fewer infants in the breastfed group required pharmacotherapy for neonatal abstinence syndrome, but this was not a statistically significant finding. Infant plasma methadone concentrations obtained on day 14 of life were low, uniformly detected among all samples, and were unrelated to maternal methadone dose, maternal plasma methadone concentrations, and breastfeeding. Further, infant plasma methadone concentration was not related to the infant's need for pharmacotherapy for NAS or NAS scores. This research demonstrated that concentrations of methadone in breastmilk, even at peak maternal plasma methadone levels, are low in the perinatal period.

Methadone; Plasma, Breast Milk

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