Pharmacokinetic Modeling of Plasma and Salivary Caffeine Circulation in Infants Receiving Extended Caffeine Therapy for Intermittent Hypoxia Treatment

Xiaoxi Liu¹, Tian Yu¹, Nicole R. Dobson², Betty L. McEntire³, Robert M. Ward¹, Michael G. Spigarelli¹, Carl E. Hunt⁴, Catherine MT Sherwin¹*

¹Department of Pediatrics, School of Medicine, University of Utah, Salt Lake City, Utah, ²Pediatrics, Tripler Army Medical Center, Honolulu, HI, ³American SIDS Institute, Naples, FL, ⁴Pediatrics, Uniformed Services University, Bethesda, MD, United States

Objectives: To develop a novel plasma/salivary caffeine recirculation model and explore the potential application of salivary caffeine measurement as a surrogate for caffeine therapeutic monitoring.

Methods: Preterm infants were enrolled in a study evaluating the effects of extended caffeine on intermittent hypoxia. Caffeine was administered orally to patients and paired salivary and plasma samples were taken. Caffeine concentrations in salivary and plasma samples were analyzed by a validated high performance liquid chromatography method. The PK model was developed using NONMEM 7.3.

Results: A total of 29 infants were included with median (5-95th quantiles) gestational age of 28 weeks (25 – 31 weeks), postnatal age of 7 weeks (3 – 12 weeks) and body weight of 2100 g (1600 -2567 g). Caffeine PK in plasma and saliva was simultaneously described by a three-compartment recirculation model with an additive error model. The final parameter estimates (95% confidence interval) of plasma clearance (CL1), salivary clearance (CL2), plasma volume of distribution (V1) and salivary volume of distribution (V2) were 0.0159 L/h (0.0137 – 0.0181 L/h), 0.0058 L/h (0.0054 – 0.0062 L/h), 0.439 L (0.311 – 0.567 L), 0.0088 L (0.0022 - 0.0154 L). The salivary secretion rate (CL3) and caffeine absorption rate (KA) were fixed to 0.006 L/h and 1.48 /h, respectively, based on literature data. Current body weight, birth weight, gestational age, postmenstrual age and postnatal age were not significantly correlated with any PK parameters.

Conclusion: Caffeine PK in saliva and plasma was well described by a three-compartment recirculation model. Future studies will utilize this model to investigate the feasibility of using salivary caffeine concentrations to predict plasma caffeine levels.