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Early Versus Late Caffeine and/or Non-Steroidal Anti-Inflammatory Drug (NSAIDs) on Biomarkers of Lung Inflammation in Neonatal Rats Exposed to Intermittent Hypoxia

Hypothesis: Caffeine and NSAID co-treatment has synergistic benefits for reducing IH- induced inflammation in the neonatal rat lungs and early postnatal treatment during IH is more beneficial than late treatment during reperfusion/reoxygenation.

Methods Used: Newborn rats (n=18/group) were exposed to brief hypoxia (12% O₂) during hyperoxia (50% O₂) from birth (P0 to P14) or room air (RA). For early, the pups were administered: 1) a single daily IP injection of caffeine citrate (Cafcit, 10 mg/kg loading on P0, followed by 5 mg/kg maintenance from P1-P14); 2) ketorolac topical ocular solution in both eyes from P0 to P14; 3) ibuprofen (Neoprofen, 10 mg/kg loading dose on P0 followed by 5 mg/kg/day on P1 and P2); 4) caffeine+ketorolac co-treatment; 5) caffeine+ibuprofen co-treatment; or 6) equivalent volume saline. On P14, animals were placed in RA with no further treatment. For late, the pups received similar treatments from P15-P17 (ibuprofen) or P15-P21 (caffeine and/or ketorolac). At P21, lungs (n=6/group) were assessed for growth and biomarkers of inflammation (IL-1, TNF α , IL-6, IL-10).

Results: Neonatal IH resulted in reduced weight accretion and lung/body weight ratios in both early and late groups. Early ibuprofen was beneficial for preserving bodyweight accretion and lung/bodyweight ratios. All late treatments were beneficial. Similarly, early caffeine/NSAID co-treatment resulted in effective decreases in pro-inflammatory cytokines (IL-1B, TNF-alpha, and IL-10) compared to late treatments.

Conclusions: Our data show that neonatal IH is deleterious to lung and body growth. Early caffeine with or without ibuprofen is preferable, and confer synergistic effects for reducing IH-induced lung inflammation. The anti-inflammatory effects of caffeine may explain in part, its beneficial effects on the decreased risk for bronchopulmonary dysplasia.