Title of Abstract:

Inhaled Sildenafil Reduces Pulmonary Hypertension and Lung Injury in a Postnatal Growth Restriction Neonatal Rat Model

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Abstract Description:

Introduction:

Pulmonary hypertension (PH) increases morbidity and mortality in premature infants with bronchopulmonary dysplasia (BPD). Postnatal growth restriction (PNGR) induces PH in neonatal rats, with development of right ventricular hypertrophy (RVH), pulmonary vascular remodeling, and impaired developmental outcome. Subcutaneous sildenafil attenuates PH in hyperoxia-exposed neonatal rats, although large injection volumes are required. We hypothesized that low dose intranasal sildenafil will attenuate the hallmarks of PH and improve learning in growth restricted neonatal rats.

Methods:

Sprague Dawley rat pups were randomized at birth to litters with normal milk intake (10 pups) or PNGR (17 pups). From birth through day 14, half the pups received 1.3mg/kg inhaled sildenafil (Revatio®) every 24 hours. On day 14, echocardiography was performed to determine PH by indirect assessment of pulmonary artery pressures (PAP) [pulmonary acceleration time (PAT)/ejection time (ET), which inversely correlates with PAP]. Fulton's index (right ventricular weight/left ventricular plus septal weight) was quantified to assess RVH. Some pups were euthanized for lung analysis by H&E and immunohistochemistry for von Willebrand Factor (vWF). Remaining pups underwent cognitive testing via T-maze at 28 days.

Results:

The PAT:ET ratio was significantly lower (evidence of higher PAP) in PNGR rats than their control counterparts (0.24+0.03 vs 0.31+0.02), with improvement in sildenafil treated pups (0.27+0.03). Fulton's index was significantly increased in PNGR rats compared to normal intake rats (0.29±0.09 vs 0.20±0.05), but this finding was attenuated following inhaled sildenafil treatments (0.19+0.04). Increased Fulton's index was secondary to both a significant increase in right ventricular weight and a significant decrease in left ventricular weight, with beneficial effects of sildenafil noted in both ventricles. Sildenafil significantly attenuated the decrease in the number of small pulmonary vessels but did not alter increased medial wall thickness in growth restricted rats. Growth restricted rats scored lower on the T-maze than control rats (2.7+1.5 vs 3.4+1.3), but Sildenafil improved test scores (3.8+1.3).

Conclusions:

Daily, low-dose inhaled sildenafil protects the developing neonatal lung, heart, and brain from the adverse effects of PNGR in a neonatal rat model of PH. This mode of administration may improve long-term outcomes of premature infants with PH and BPD, and may provide an alternative to intravenous or enteral sildenafil delivery with less risk of undesirable systemic effects.

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