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Combination therapy of brain natriuretic peptide and sildenafil attenuates pulmonary hypertension in rats

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Background: Pulmonary arterial hypertension (PAH) is a lethal disease characterized by changes in pulmonary vascular structure and function. We tested the hypothesis that Sildenafil, a phosphodiesterase 5 inhibitor, and brain natriuretic peptide (BNP), a guanosine cyclase stimulator, in combination synergistically attenuates PAH when compared to individual therapy in rats through different mechanisms to increase cGMP while minimizing systemic side effects.
Methods: Adult male Sprague-Dawley rats were subcutaneously injected with monocrotaline (n=30, 50 mg/kg). After approximately 5 weeks, rats were anesthetized and instrumented to measure systemic pressure (MAP) and right ventricular systolic pressure (RVSP) during infusions of vehicle solution (n=5), intravenous Sildenafil (84 mg/kg/min; n=8), and intravenous BNP (100 ng/kg/min; n=7) alone and a combination of Sildenafil and BNP (n=10).
Results: Sildenafil alone decreased RVSP (-17 ±13.2 mmHg) and had a relatively minimal effect on MAP (-4±9.9 mmHg). BNP decreased RVSP (-19±14 mmHg) but also significantly effected MAP (-11±15.3mmHg). Combination therapy with Sildenafil and BNP lowered RVSP (-20±18.7 mmHg), however it also induced the greatest systemic hypotensive effect (MAP = -19±9.9 mmHg).
Conclusion: The combination of Sildenafil and BNP, at these doses, significantly attenuates monocrotaline-induced pulmonary hypertension. However, compared with individual treatment, there is no significant difference in effect on RVSP. Furthermore, additive systemic side effects are too significant to consider combination therapy safe. With a different dosing regime, this combination is a potentially viable option in the treatment of patients with PAH.