

EFFECTS OF TREPROSTINIL SODIUM IN A MONOCROTALINE-INDUCED RAT MODEL OF PULMONARY HYPERTENSION

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ABSTRACT

Treprostinil is a prostacyclin analog currently used in the treatment of pulmonary hypertension. Although clinical studies show treprostinil to be a successful therapy for pulmonary hypertension, little information exists concerning the effects of treprostinil treatment *in vivo*. The purpose of this study is to elucidate the effects of treprostinil on right ventricular systolic pressure (RVSP), right ventricular hypertrophy and vascular remodeling in a rat model of MCT-induced pulmonary hypertension. Male, Sprague-Dawley rats were randomized to one of four treatment groups; control, monocrotaline (MCT) only, MCT with treprostinil treatment (MCT/TRE), and treprostinil treatment only (TRE). At the beginning of the experiment, rats received a one-time subcutaneous dose of MCT (60 mg/kg) or saline. Rats were then administered either treprostinil or placebo for 28-days. After 28-days of treprostinil treatment, we recorded RVSP and right ventricular size. In addition, paraffin embedded left whole lung tissues were used for morphometric analysis and right whole lung tissues were snap frozen in liquid nitrogen for protein analysis. As expected, MCT exposure caused a significant increase in RVSP and right ventricular hypertrophy. Morphometric analyses also indicated that MCT-exposure led to medial wall thickening of the pulmonary vasculature. Neither low-dose (10 ng/kg/min) nor high-dose (150 ng/kg/min) treprostinil therapy attenuated elevations of RVSP and right ventricular hypertrophy in pulmonary hypertensive rats. In addition, there was no attenuation of medial wall thickening when MCT-exposed rats also received

treprostinil treatment. Finally, treprostinil significantly lowered PPAR- γ protein expression in MCT-exposed rats. In conclusion, we demonstrated that increases in RVSP, right ventricular hypertrophy and vascular remodeling associated with MCT-induced pulmonary hypertension are not attenuated with treprostinil therapy.

Additionally, we found that treprostinil attenuated the induction of PPAR- γ protein levels in whole lung homogenates of MCT-exposed rats. Although we have not yet established that PPAR- γ is an important therapeutic target for pulmonary hypertension, we speculate that further investigation of its role could reveal a mechanism in which PGI₂ elicits its effects on the pulmonary vasculature.