AN EXPLORATORY EFFICACY STUDY OF PULMONARY ARTERIAL PRESSURE IN SPRAGUE-DAWLEY RATS

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ABSTRACT

The objective of the study was to evaluate the pulmonary artery pressure (PAP) of Sprague-Dawley rats, equipped with a telemetry implant, when administered U-44069, a PGH_2 analog, similar to endogenously formed thromboxane A_2 which can be titrated to induce the desired degree of pulmonary vasoconstriction, 3 times a day.

Prior to the study, rats had a subcutaneous telemetry device implanted and the catheter was placed in the right ventricle and advanced into the pulmonary artery.

Rats received intravenous infusions of U-44069 at a formulation concentration of 0.5 mg/mL, administered for 15 minutes at a dose rate of 10 mL/kg/hr, 3 times per day, separated by approximately 1 hour. Additional control rats were kept in the restrainer used during infusions and followed the same regimen (i.e. 3 times per day).

The PAP increases were similar after each administration, although slightly less significant increases were observed after the second and third administrations. However, there were still significant increases in PAP of at least 51%, and therefore, it is considered that multiple daily administrations are appropriate for this model.

In addition, there were no significant changes in PAP in control animals, therefore the restraint procedure is not considered to have an impact on the evaluation and interpretation of the data with this model.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a disease caused by the hardening and narrowing of the pulmonary arteries. This requires the heart to work harder to pump blood through the pulmonary arteries and lungs. Over time, the right ventricle will become weak and strained and may ultimately lead to heart failure (NHLBI website).

There is no cure to PAH, however there are treatments available and other medications currently under development. To evaluate the efficiency of new drugs on PAP, an animal model was developed in Sprague-Dawley rats, equipped with a telemetry implant, when administered U-44069 for 3 times a day.

U-44069 (9,11-dideoxy-9α,11α -epoxymethanoprostaglandin $F_2\alpha$) is a PGH_2 analog, similar to endogenously formed thromboxane A2 and can be titrated to induce the desired degree of pulmonary vasoconstriction (Sandifer et al., 2005).

EXPERIMENTAL DESIGN

Group Number	Group Designation	Target Dose Level (mg/kg/dose)	Dose Formulation Concentration (mg/mL)	Dose rate (mL/kg/hr)	Number of Animals (Male)
1	Control	0	0	0	3
2	Treated	1.25	0.5	10	3

Prior to the study, rats had an HD-S21 telemetry device (Data Sciences International) (Figure 1) implanted intraperitoneally and a catheter was placed in the right ventricle and advanced into the pulmonary artery. The second catheter was inserted into the aorta to measure systemic pressure.

Rats received intravenous infusions of U-44069 at a formulation concentration of 0.5 mg/mL, administered for 15 minutes at a dose rate of 10 mL/kg/hr, 3 times per day, separated by approximately 1 hour. Additional control rats were kept in the restrainer used for infusions and followed the same regimen (i.e. 3 times per day).

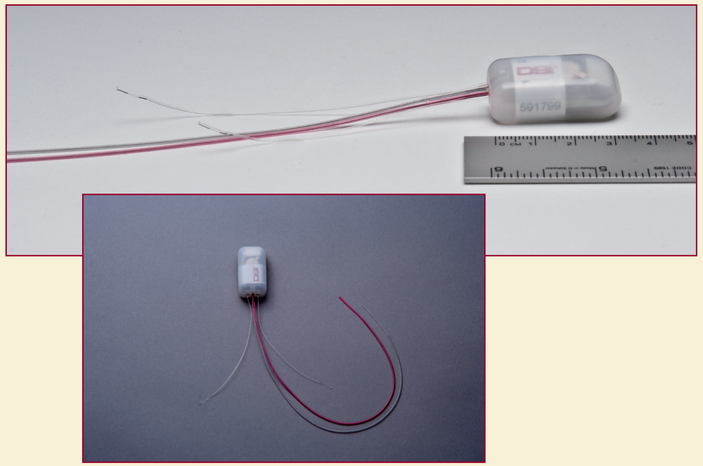

Figure 1: HD-S21 Telemetry Device

PREPARATION OF TEST SYSTEM

The animal was sedated and the ventral abdomen was shaved and scrubbed. A midline incision was made through the abdominal wall. The liver was retracted and an incision was made through the diaphragm. The diaphragm was retracted and the pericardium was broken. An anchor suture was placed on the right ventricle of the heart to retract it. A purse string suture was then placed on the right ventricle. The heart was punctured and the catheter was placed inside the right ventricle and advanced into the pulmonary artery. The catheter was sutured to the heart. The diaphragm was sutured closed. The chest was evacuated of all air to resume negative pressure. The intestines were then retracted and the aorta was isolated. An occlusion suture was placed just caudal to the renal vein and cranial to the iliac bifurcation. The aorta was punctured and the second catheter was inserted and advanced to the cranial occlusion suture. The catheter entry site was sealed with Vetbond and the catheter was secured with a fiber patch. The occlusion sutures were removed, the retraction was removed, and the abdomen was irrigated with warm saline. The transmitter was then placed in the abdominal cavity and sutured to the side of the abdominal wall. The abdominal wall was closed. The skin was stapled closed.

RESULTS AND DISCUSSION

There were no significant changes in PAP in control animals. Changes observed were considered to be within normal variations.

On all reported occasions, the IV dosing of U-44069 increased the PAP to at least 150% of the baseline. The effects following the second and third dosing occasions were slightly lower than recorded following the first dosing, however there was still a significant increase in PAP.

The PAP gradually went back to normal ranges shortly after the infusion was completed.

A summary of the data is presented in Table 1 and representative graphs of control and treated animals are presented in Figure 2.

The administration of U-44069 had no effect on the systemic pressure (data not shown).

Table 1: Peak PAP (mmHg) obtained during IV infusions

	Control			U-44069		
	1001A	**1002A**	**1003A**	**2001A**	**2002A**	**2003A**
Baseline	26.7	30.5	52.7	28.3	34.1	43.9
Rx1	32.6	37.5	57.9	49.9	62.0	75.4
Rx2	26.0	35.8	51.8	49.3	59.3	66.4
Rx3	27.4	35.3	55.1	47.0	59.0	67.9
Percent Change from Baseline						
Rx1	122.2	123.2	109.8	176.2	181.7	171.8
Rx2	97.4	117.3	98.3	174.3	173.8	151.3
Rx3	102.6	115.8	104.6	164.9	172.7	154.8

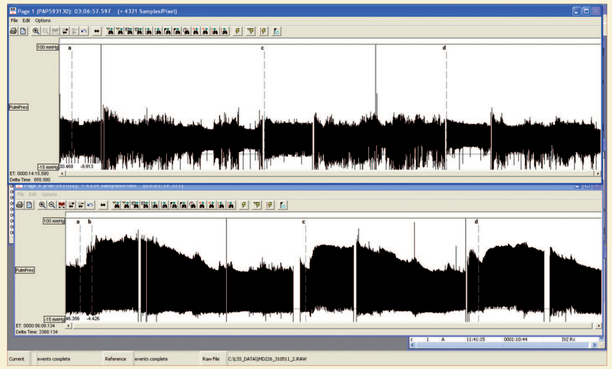

Figure 2: Representative graphs of PAP of control (top) and treated (bottom) animals

CONCLUSION

The PAP increases were similar after each administration of U-44069, although slightly less significant increases were observed after the second and third dosings. However, there were still significant increases in PAP of at least 51%, and therefore, it is considered that multiple daily dosings are appropriate for this model.

In addition, there were no significant changes in PAP in control animals, therefore the restraint procedure is not considered to have an impact on the evaluation and interpretation of the data with this model.

Based on the results obtained, this model is considered to be valid for the evaluation of PAP.

REFERENCES

National Heart, Lung and Blood Institute (NHLBI) : http://www.nhlbi.nih.gov/health/health-topics/topics/pah/

Sandifer, B.L., Brigham, K.L., Lawrence, E.C., Mottola, D., Cuppels, C. and Parker, R.E. 2005. Potent effects of aerosol compared with intravenous Treprostinil on the pulmonary circulation. J. Appl. Physiol. 99: 2363-2368.