

### **A. Study Purpose and Rationale**

Pulmonary Hypertension is a rare, progressive, life-threatening disease with a very high mortality<sup>3</sup>. There are no FDA approved drugs for PH in children with most treatments being extrapolated from adult studies. Pediatric PH shares many similarities with adult PH however there are also many unique clinical features including development of vascular bed, prevalence of different PH subtypes, and different mortality data.<sup>4</sup> Sildenafil is a selective phosphodiesterase 5 inhibitor that has been used in the treatment of pulmonary arterial hypertension (PAH) in the pediatric population since 2005.<sup>5</sup> This use is largely based on adult studies as there is limited evidence regarding the safety and efficacy of sildenafil in children. In 2005 there were case reports of efficacy of sildenafil in treatment of pulmonary hypertension in the pediatric population at the same time as sildenafil was FDA approved for treatment of adults.

There was then a pilot study of 14 pediatric patients in 2005 showing some efficacy and pharmacokinetics data.<sup>6</sup> Most recently a randomized double blind placebo controlled dose ranging study of oral sildenafil by Barst et al was published in 2011. This larger study showed marginally significant efficacy in medium and high dose sildenafil with no efficacy with low dose sildenafil. In a follow up study there was also found to be increased mortality in the group randomized to receive the higher dose of sildenafil<sup>2</sup>. This prompted the FDA to place a black box warning on the treatment of PAH with sildenafil in children.<sup>1</sup> Given the high mortality associated with pulmonary hypertension and the limited drug choices more information is needed regarding the safety and efficacy of sildenafil in the treatment of pulmonary hypertension in children. Describing our experience with sildenafil in over 100 patients with PAH will help to contribute to the limited data on this subject.

### **B. Study Design and Statistical Analysis**

Hypothesis: Treatment of Pulmonary Hypertension (PH) with oral sildenafil in the pediatric population will likely improve clinical outcome measures of PH as measured by symptom improvement as well as objective clinical data include echocardiographic and cardiac catheterization measurements.

Retrospective longitudinal cohort study analyzing data from 105 patients treated with sildenafil age 1-17. Data will be collected and outcomes will be examined pre-sildenafil (within 3 months), and post-sildenafil (1-3 months, 6 months and 12 months)

Gender:

Females: 56%

Males: 44%

Age:

1-7: 48%

8-17: 52%

Statistical analysis will include a paired t-test comparing mean pulmonary artery pressure (mPAP), pulmonary vascular resistance index (PVRI), cardiac index (CI) and 6 minute walk distance before and after sildenafil treatment, using each patient as his own control. A chi-squared analysis will be used to compare functional class before and after sildenafil treatment.

In statistical analysis alpha will be set as  $<0.05$ , power=80%.

An analysis of background data will also be performed to better describe our patient population being treated with sildenafil. Some of these measurements will include age, sex, race, duration of PH diagnosis prior to initiation of sildenafil, subtype of PH, and comorbidities. Duration of sildenafil treatment, dose of sildenafil and any adverse events will be examined. Analysis will also be performed with subgroups looking at the dose of sildenafil, as well as the efficacy of sildenafil in various subgroups based on etiology of PH including patients with congenital heart disease, bronchopulmonary dysplasia (BPD) and congenital diaphragmatic hernia (CDH). Analysis will also include concomitant use of other medications used to treat PH. Other outcomes that will be measured include hospitalization, initiation of other medications, transplant and death.

**C. Study Procedure**

This will be a descriptive retrospective cohort study with data analysis performed on 105 pediatric patients treated with sildenafil from 2005-2013. Chart review will be performed on these 105 patients to obtain background data, clinical information and outcome measures.

**D. Study drugs**

Retrospective study examining oral sildenafil treatment.

**E. Medical device**

Not applicable

**F. Study Questionnaires**

Not applicable

**G. Study Subjects**

105 patients aged 1-17 treated for PH at Columbia University Medical Center with oral sildenafil between 2005-2013.

**H. Recruitment of subjects**

Retrospective study-not applicable.

**I. Confidentiality of the study**

During data collection the name and MRN of each patient will be available to the investigators. After data collection is complete data will be de-identified.

**J. Potential conflict of interest**

None

**K. Location of study**

Columbia University Medical Center

**M. Potential benefits**

This study will add to the fund of knowledge regarding safety and efficacy of sildenafil in the treatment of pulmonary hypertension, resulting in more effective treatment of PH in the pediatric population. Given the recent controversy regarding treated of PH with sildenafil in the pediatric population, this study will add to the limited data on the subject.

**N. Alternative therapies**

Not applicable

**O. Compensation of Subjects**

Not applicable

**P. Costs to Subjects**

Not applicable

**Q. Minors as Research Subjects**

The research consists of chart review and data analysis of use of sildenafil in children. The children's treatment will not be in any way changed because of this study. The results of the study may aid in further understanding the use of sildenafil in children

**R. Radiation or Radioactive Substances**

Not applicable

**References:**

1. Abman et al. Implications of the U.S. Food and Drug administration Warning against the Use of Sildenafil for the Treatment of Pediatric Pulmonary Hypertension. *Am J Respir CritCare Med* Vol 187, Iss.6, pp572-575, Mar 15, 2013.
2. Barst et al. A Randomized Double-Blind, Placebo-Controlled, Dose-Ranging Study of Oral Sildenafil Citrate in Treatment-Naïve Children with Pulmonary Arterial Hypertension. *Circulation* 2012;125:324-334
3. Galie et al. Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension. *N Engl J Med* 2005; 353: 2148-2157.
4. Karatza et al. Safety and efficacy of Sildenafil therapy in children with pulmonary hypertension. *International Journal of Cardiology* 100 (2005) 267-273.
5. Raja et al. Treatment of Pulmonary Arterial Hypertension with Sildenafil: From Pathophysiology to Clinical Evidence. *Journal of Cardiothoracic and Vascular Anesthesia* Vol 20, No 5 (October) 2006 pp 722-735.

6. Tilman et al. Beneficial effect of oral sildenafil therapy on childhood Pulmonary Arterial Hypertension: Twelve-Month Clinical Trial of a Single-Drug, Open-label pilot study. *Circulation*, 2005;111:3274-3280.