The use of Sildenafil in Patients with COPD Exacerbations Eequiring Mechanical Ventilation

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A. Study Purpose and Rationale

The purpose of this study is to investigate whether sildenafil has a clinical benefit if given to patients with COPD exacerbations requiring mechanical ventilation.

Phosphodiesterase type 5 is the predominant phosphodiesterase isoform in the lung that metabolizes cGMP. Phosphodiesterase type 5 has been shown to be elevated in pulmonary hypertension. Cyclic GMP is a second messenger which enhances nitric oxide mediated vasodilation. Sildenafil citrate increases cGMP within vascular smooth muscle cells resulting in relaxation and vasodilation. In patients with pulmonary hypertension, this leads to vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilation in the systemic circulation. Nazzareno, et al. showed in a randomized, double-blind, placebo controlled study that sildenafil improves exercise capacity and hemodynamics in patients with symptomatic pulmonary arterial hypertension (NEJM, Nov 2005).

Pulmonary hypertension is commonly seen in end stage COPD. It is the strongest marker of morbidity and mortality in this disease. Historically it has been thought that pulmonary hypertension in COPD is directly related to chronic hypoxia and/or destruction of the pulmonary vascular bed by emphysema. However, more recent studies have shown that there may also be direct effects of smoke on the pulmonary vasculature which drive vascular remodeling similar to that seen in other causes of arterial pulmonary hypertension. Therefore, new treatments that target vascular relaxation and remodeling should be studied in patients with COPD. One example of these treatments is sildenafil. Most other drugs used in pulmonary hypertension have adverse effects in terms of safety, tolerability, and drug delivery (i.e.: IV infusion). Sildenafil is a well tolerated oral medication that is easy to give and has few adverse effects. It has been well studied in humans with erectile dysfunction and pulmonary hypertension.

In 87% of severe COPD patients the mean arterial pressure is not elevated (between 20 and 35 mm HG). However, during exercise or during an acute exacerbation, the mean arterial pressure increases remarkably. Elevated mean arterial pressures are directly correlated with mortality. Therefore, there seems to be a theoretical benefit to treating pulmonary hypertension during an acute exacerbation to decrease morbidity and mortality. Morbidity and mortality in patients with COPD exacerbations who require mechanical ventilation is also correlated to duration on the ventilator. This study wants to look at whether treating patients with COPD exacerbations and acute respiratory failure with sildenafil reduces the duration of mechanical ventilation.

B. Study Design and Statistical Analysis

We will conduct a prospective, randomized, double-blind, placebo-controlled, multi-center trial looking at the effects of sildenafil in patients with COPD exacerbations requiring mechanical ventilation. We will randomly assign 260 patients with COPD exacerbations who require mechanical ventilation in the ICU to receiving placebo or sildenafil, in addition to standard therapy. Sildenafil will be given at 20 mg doses every 8 hours via nasogastric tube. The primary outcome will be duration of mechanical ventilation measure in days. The effect expected to be seen is a decrease by 1 day of mechanical ventilation. Treatment failure will be considered if a patient is not extubated by day 21. Patients who die on the ventilator will be considered treatment failures and will be given a 21 day value. The secondary outcomes that we will look at are ICU mortality and in-hospital mortality.

The sample size was calculated using a t-test power analysis. Nevins, et al. showed in a cohort study that COPD patients who require mechanical ventilation have a mean duration of 5.3 +/- 10.9 days,

with a medial of 1.1, and interquartile values of 03. and 4. Based on these interquartile values, we calculated the standard deviation to be 2.77. Using the unpaired t test equation, the number of people needed in each group was 124.

The primary outcome measured in days is expected to be have skewed distribution because most patients will be extubated within the first few days but some may remain intubated all 21 days. Given the skewed distribution, a non-parametric analysis (Wilcoxon Ranksum test) will be used to analyze the primary outcome. The secondary outcomes are both categorical variables; therefore a chi-square test will be used for the statistical analysis.

C. Study Procedure

Giving sildenafil for COPD exacerbations is not standard of care. However, given the theoretical benefit, it may have significance in the patient's clinical management. It is an easy drug to give and has been very well tolerated in humans for other disease processes. It will be given through a nasogastric tube, which an intubated patient will require anyway for enteral feeding. No additional catheters or instruments are required and the patient will not experience pain or discomfort. If the patient becomes hypotensive (i.e. MAP < 65) the study drug or placebo will be held until blood pressure returns to a normal level. Receiving this study drug does not interfere with the patient receiving adequate care and the physicians in charge are blinded as to who is receiving study drug vs. placebo. Each subject will participate in the study for as long as they remain on the ventilator or for a total of 21 days (whichever one comes first). We expect to enroll 50 patients per center, per year with a total of four centers. Therefore, the duration of the study is expected to be about 1.5 to 2 years.

D. Study Drugs

Sildenafil is currently approved for both erectile dysfunction and pulmonary hypertension. The route of administration and dosage regimen will be the same as the one used in the pulmonary hypertension trials. Nazzareno, et al. showed in their study that all sildenafil doses reduced mean pulmonary arterial pressures, therefore the lowest dose will be used for this study (20 mg p.o. q8h). The main difference is the drug in this study will be given via nasogastric tube, instead of orally. The known side effects are mild and include flushing, dyspepsia, diarrhea, rash and headache. They are expected to be seen in about 4-10% of the study population.

E. Study Subjects

The study subjects will be patients with COPD who present with acute respiratory failure and require mechanical ventilation despite maximal medical treatment. The inclusion criteria are prior history of COPD either by spirometry (FEV1<50%) or by history and clinical correlation (i.e. smoking history, hyperinflated lungs on CXR, emphysema on chest CT). Acute respiratory failure will be defined as respiratory rate > 35 breaths/min, severe dyspnea, severe respiratory acidosis (pH < 7.25 and pCO2 > 65), and use of accessory muscles.

Exclusion criteria will include current cardiac ischemia or CAD requiring nitroglycerin, malignant hypertension (since may require nitroprusside), CHF, hypotensive shock, nosocomial pneumonia, other chronic pulmonary diseases (ex: lung cancer, IPF, sarcoid), liver failure (drug is hepatically cleared), gi bleeding, and malignancy.

F. Recruitment of Subjects

In order to recruit study subjects, a copy of the protocol and consent form will be sent to PMDs and pulmonary clinics in the community. The PMDs should explain the study to eligible patients and get consent when the patient is not critically ill. It is understood that the patient will only enrolled in the

study if faced with an acute exacerbation requiring mechanical intubation and ICU care. Therefore, most patients who consent for the study will never be enrolled in the study.

G. Confidentiality of Study Data

All study data will be coded, and a unique code number will be used for all study subjects. Data will be stored in a secure location and will only be accessible to the investigators.

H. Potential Risks

The study drug has been approved for human used and is well studied and well tolerated. The main adverse effects are flushing, rash, headache, dyspepsia, and diarrhea. There is also a risk of lowering blood pressure, usually not clinically significant. If a patient in the study has a lowering of BP (MAP < 65) the study drug or placebo will be held until deemed appropriate by the ICU physician. Standard treatment will not be withheld from study subjects. There is a 50% chance of receiving placebo instead of the active treatment. There is also a slight risk that the subjects condition may worsen as a result of the study drug.

I. Potential Benefits

Study subjects may or may not benefit as a result of participating in the study. However there is a potential benefit of improvement in clinical outcome and decrease in number of days on the ventilator.