Efficacy of Terlipressin + Milrinone vs. Milrinone in Ionotropic Assisted Diuresis
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A. Study Purpose and Rationale

Congestive heart failure (CHF) can be defined as an inability of the heart to maintain adequate forward flow leading to difficulties with fluid balance. Over 5 million people have congestive heart failure, and over 900,000 hospitalizations per year are for exacerbation of congestive heart failure, costing the health care system millions of dollars annually in their care[1].

Patients with CHF are usually managed on a combination of medications including afterload reducers and diuretics. As their disease progresses, they often become less responsive to these medications, and end up in a diuretic-refractory state of volume overload. These patients are often started on milrinone, a phosphodiesterase inhibitor. Milrinone increases cyclic-AMP and cyclic-GMP in vascular smooth muscle, thereby increasing myocardial contractility. By increasing pump function, patients are better able to maintain euvolemia. However, in patients with end stage heart failure, milrinone often causes vasodilation and hypotension[2]. This side effect of milrinone often limits the use of other therapeutic interventions. Medications are often held as systolic blood pressure is low, and it would be dangerous to further lower blood pressure with a diuretic or ACE inhibitor. These medications, however, have a proven symptomatic (in the case of diuretics) and mortality (for ACEI) benefit for patients with CHF exacerbation. Limiting their use often prolongs hospitalization, requires ICU transfer for blood pressure augmentation, and often necessitates further mechanical interventions (i.e. placing a left ventricular assist device or intra-aortic balloon pump). Use of a pressor agent to increase systolic blood pressure would allow more aggressive titration of diuretics and other medications, expediting the patients return to dry weight, reducing hospital stay, and saving them from more invasive measures.

I hypothesize that starting a concomitant medication to increase blood pressure with milrinone will increase response to medications and enable more effective diuresis. In several case reports and small studies, arginine vasopressin (AVP) was shown to increase arterial pressure and urine output in patients with CHF on milrinone[3]. AVP inhibits activation of adenylate cyclase and guanylate cyclase in vascular smooth muscle, thereby directly inhibiting the action of milrinone, decreasing vasodilation and increasing blood pressure. Terlipressin is a synthetic analog of vasopressin, which has been successfully used to treat vasodilatory shock in Europe[4]. Both AVP and terlipressin have been showed to cause coronary artery ischemia at supratherapeutic doses, therefore only pts with non-ischemic cardiomyopathy will be included in this study[5]. Advantages of terlipressin over AVP are many. Terlipressin has a longer half-life (6 hours vs. just minutes for vasopressin), allowing to be delivered as an IV bolus instead of a continuous infusion. Patients often have rebound hypotension with the discontinuation of vasopressin infusion, requiring a slow taper. This effect has not been seen with terlipressin. In addition, long-term delivery of AVP often requires placement of a central venous catheter, an invasive procedure, as well as ICU transfer. The use of terlipressin instead of vasopressin will avoid these risks to the patient, and may be equally as effective in maintaining arterial blood pressure during milrinone infusion. This will be randomized,

double blinded control trial to evaluate the efficacy of terlipressin combined with milrinone vs. milrinone alone in the treatment of volume overload in patients who present with CHF exacerbation.

B. Study Design and Statistical Analysis

This will be a randomized, double blinded control trial evaluating the efficacy of terlipressin + milrinone vs. milrinone + placebo in ionotropic assisted diuresis. The study period will be four days. This duration is based on prior studies which estimate the average length of hospitalization for diuresis between 3.5 and 6 days[6]. The primary outcome will be total weight loss in kilograms at the end of the study period. Patients will be randomized via the research pharmacy to receive terlipressin vs. placebo with the initiation of milrinone. The study drug will be given for 4 days. The primary outcome will be total weight loss in kilograms after 4 days. Preliminary data suggests that the use of a vasopressor with milrinone doubles UOP[3], however as these were very small studies over short periods of time, therefore a more conservative estimate will be used for this study. The anticipated effect will be estimated as 1 kg greater decrease in weight loss in the terlipressin + milrinone group. Using an unpaired t-test for continuous variables, with a standard deviation of 1kg, n=17 with a power of 80%, testing at p=0.05. For this study, we will aim to recruit a total of 40 patients, 20 in each arm.

C. Study Procedure

After obtaining informed consent, patients will be evaluated for participation in the study based on the following inclusion/exclusion criteria.

Inclusion criteria:
-Age>18 years
-Documented ejection fraction<35% by echocardiography
-signs of volume overload on exam (increased jugular venous distension >5cm or increased central venous pressure, crackles on lung exam, LE edema)
-resistant to maximal IV diuresis, not including a lasix drip
->5kg above dry weight
-cardiac catheterization with no evidence of obstructive coronary artery disease

Exclusion criteria:
-Ischemic cardiomyopathy or h/o MI, angina, CAD
-on ionotropes or pressors in the past 24 hours
-signs of shock (SBP<80mmHg, HR>120, T>38.3)
-oliguric renal failure
-history of life-threatening arrhythmia (ventricular tachycardia/fibrillation)

Once patients are deemed eligible for the study, and informed consent is obtained, they will be randomized into one of two arms. Arm 1 will be milrinone via IV infusion + terlipressin as an IV bolus q 6hrs. Arm 2 will be milrinone via IV infusion + placebo (injection of 0.9 normal saline) as an IV bolus q6hr. All patients will be on a cardiac floor with telemetry monitoring. Subjects will remain on their respective treatments for 96

hours. Housestaff giving IV bolus medication will be blinded. Subjects will be weighed prior to enrollment into the study and q24hrs while in the study. Hourly urine output will be measured by nursing staff. Blood pressure and heart rate will be measured q8hours. The protocol will be stopped if the patient develops any signs of ischemia, arrhythmia, hypotension, fever, signs of infection, worsening volume overload or allergic reaction. All patients will have daily blood draws, as per usual standard of care in hospitalized patients. Lab values to be measured will include: Serum chemistries (including sodium, potassium, chloride, bicarbonate, BUN, creatinine, and glucose), magnesium, phosphorus levels; complete blood count (including white blood cell count, hemoglobin, hematocrit, and platelet count), liver function tests (total protein, albumin, total bilirubin, direct bilirubin, AST, ALT, and alkaline phosphatase). All patients will have daily electocardiograms to monitor for arrhythmias or signs of ischemia. All patients will have q12hr physical exam to assess for ischemic changes.

All patient information (including age, gender, race, medical history, etc) will be kept in a separate, password protected file on a computer in an office that will be locked after business hours and only accessible by members of the investigational team.

D. Study Drugs

Milrinone is a positive ionotrope and vasodilator. It is FDA approved for the short-term treatment of congestive heart failure. It has been shown to increase cardiac output and decrease pulmonary capillary wedge pressure in patients with CHF. Milrinone does increase the frequency of ventricular tachycardias, therefore, all patients should be monitored continuously on telemetry. It also can decrease AV node conduction time, predisposing patients in atrial fibrillation to rapid ventricular response, however, this is amenable to pharmacologic treatment with either digoxin or rate controlling agents. Other, less common, side effects include headache (2.9%), hypokalemia (0.6)%, and thrombocytopenia (0.4%)[8] although none of these have been directly correlated to milrinone. It is given first via an IV loading dose of 50mcg/kg, then an continuous infusion is started between 0.375-0.5mcg/kg/min. The dose is adjusted for renal insufficiency.

Terlipressin is a synthetic vasopressin analog. It has been used in Europe and is currently undergoing Phase III trials for the treatment of hepatorenal syndrome under PDL BioPharma. It will require an investigational drug application. It acts at V-1 receptors to constrict vascular smooth muscles. It has been shown to decrease coronary blood flow only at supratherapuetic doses. Adverse effects reported include: headache, abdominal pain, cardiac arrhythmia, and hypertension[9]. This medication is given as a 1mg IV bolus (through a peripheral intravenous catheter) every 6 hours.

E. Medical Devices

No medical devices will be used for the purpose of this study.

F. Study Questionnaire

No study questionnaires will be used during this study.

G. Study Subjects

Inclusion/Exclusion criteria for the study are as follows:

Inclusion criteria:
-Age >18 years
-Documented ejection fraction<35% by echocardiography
-signs of volume overload on exam (increased jugular venous distension >5cm or increased central venous pressure, crackles on lung exam, LE edema)
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-oliguric renal failure

This study will be open to all genders, race, and ethnicity, and attempts will be made to recruit a sample representative of the current US population.

H. Randomization

Clinicians will be made aware of the study with informational flyers and presentation to the heart failure group at Columbia-Presbyterian. An investigator will be available by beeper at all times, and will be notified by the primary team when a patient is being considered for initiation of milrinone. The primary team must agree that the patient is suitable for the study and have ascertained that the patient is willing to speak with someone about the study, then a member of the investigation team will approach them. Once consent is obtained from the patient or their proxy, the research pharmacy will randomize subjects to terlipressin vs. placebo.

I. Confidentiality

Each patient will receive a unique coded identifier. All information gathered as part of this study, including lab values, vital signs, urine output, and telemetry recordings will be stored on a separate data sheet using this identifier. Data will be stored in a password protected file in a secure location.

J. Potential Conflict of Interest

No known conflict, investigators would not benefit monetarily from this study.

K. Locality of the study

Study will take place in the clinical areas of Columbia Presbyterian Medical Center, including patients in Milstein Hospital on 5 Garden South (cardiac floor) or Cardiac Intesive Care Unit.

L. Potential Risks

Subjects in this study are at risk for side effects secondary to terlipressin, including, but not limited to, coronary artery ischemia, peripheral limb ischemia, and arrhythmia. Patients with known coronary artery disease will be excluded from the study to eliminate risk. Subjects will be monitored closely for arrythmias and ischemia. Subjects are also at risk for hypotension and arrhythmia secondary to milrinone and will be monitored closely for the development of these side effects. If these risks occur, subjects will be removed from the study.

M. Potential benefit

You may or may not benefit as a result of your participation in this study. Potential benefits to society include improving treatment of patients with heart failure, decreasing hospital stay, and potentially limiting complications of hypotension, including renal insufficiency.

N. Alternative therapies

Alternative therapies include the use of AVP (arginine vasopressin), which must be delivered via continuous infusion using a central venous catheter and ICU transfer. There have been no large, randomized, controlled trials to evaluate the use of AVP with milrinone. Treatment of subjects in this study will not deviate from current standard of care.

O. Compensation to subjects

Subjects will not receive compensation for participation.

P. Costs

The subjects will not incur any additional costs as a result of study participation. The subjects insurance or, if uninsured, CPMC will pay for the costs of hospitalization and lab tests. BioPharma will provide terlipressin.

Q. Minors

No minors are involved in this study

R. Radiation or Radioactive substances

No radioactive substances or radiation will be used in the study.

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