Serum Aldosterone and Response to Spironolactone in Advanced Heart Failure

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A. Study Purpose and Rationale

Congestive heart failure (CHF), often characterized by a loss of left ventricular function, affects approximately 5 million people in the U.S and has an annual incidence of 500,000 people[1]. In addition, CBF constitutes the most common diagnosis-related group (DRG) for Medicare, and more Medicare dollars are spent on the diagnosis and treatment of CHF than any other DRG[1]. People with CFIF and decreased left ventricular ejection fraction have a reduction in their cardiac output with the development of hypotension and decreased renal perfusion. This decreased renal perfusion leads to neurohumoral activation including activation of the renin-angiotensin-aldosterone system (RAAS) [2-7] . The RAAS stimulates sodium and water retention, as well as vasoconstriction mediated directly by angiotensin-11 [4] . The net result of the activation of the RAAS is increase increased salt and water retention, increased peripheral vascular resistance, increased myocardial work and oxygen consumption and demand, and expansion for the extracellular fluid volume. This leads to volume overload and an exacerbation of pump failure with worsening of symptom and clinical state including increased rates of arrhythmia and cardiopulinonary failure[7-9]. Additionally, aldosterone is thought to be directly cardio-toxic, resulting directly in myocardial fibrosis and predisposing to fatal ventricular arrhythmias[8].

CHF carries with it a very poor prognosis and pharmacotherapy remains the mainstay of treatment and several studies have demonstrated that persistent elevation of the RAAS and other markers of neurohunioral activation are correlated with worse prognosis[5]. Current guidelines for the management of chronic CHF indicate a role for the use of a loop-diuretic, digoxin, a betaadrenergic blocker in those who can tolerate it and an angiotensin-converting enzyme inhibitor[1] The use of ACE inhibitors in the treatment of heart failure is supported by the data from the CONSENSUS trial which showed markedly decreased mortality in patients with CHF who received enalapril in addition-to standard therapy[4]. It is presumed that this benefit is related to suppression of the RAAS[4]. Unfortunately it does not appear that that use of maximal doses of ACE-inhibitors result in complete inhibition of the RAAS[10]. This is thought to be related to the generation of angiotensin II via pathways that are not dependent on the angiotensin converting enzyme and thus unaffected by ACE inhibitors 10. In addition there is non-angiotensin II associated aldosterone production 10. Given the evidence that neuroliumoral stimulus remains despite ACE-inhibition the use of a direct Aldosterone receptor antagonist (Spironolactone) was studied in the RALES trial to determine if it had an additive benefit to the use of ACEinhibitors in patients with advanced heart failure[2]. While the RALES trial did support a survival benefit for patients with advance CHF with the addition of Spironolactone to the standard medical therapy, additional data suggest that there is a marked increase in morbidity and mortality associated with severe hyperkalemia secondary to the concomitant use of ACE-1 and Spironolactone (morbidity increased from 2.4 to 11/1000 and mortality from 0.3 to 2/1000) [11].

At this time CHF remains an important source of morbidity and mortality in the US and the RAAS has a significant role in its pathophysiology. The addition of ACE-inhibition to the arniamentarium. of drugs to treat CHF has improved survival and it appears that the addition of Spironolactone may improve morbidity and mortality even ffirther but that the combination of an ACE-1 and Spironolactone carries with it the not-insignificant risk of fatal hyperkalemia[11]. However, studies suggest that not all patients on ACE-inhibitor therapy continue to have over activation of the RAAS and data indicate that only one third of patients on maximal ACE-1 therapy continue to have elevated Aldosterone levels[10] Therefore, it is possible that this subset of patients, those with elevated aldosterone

levels, despite maximal ACE-inhibition, would preferentially benefit from the addition of Spironolactone to their standard medical therapy. it is my hypothesis that it will this group who will preferentially respond to addition of Spironolactone to standard CHF treatment. If this hypothesis is true then we can target the use of Spironolactone to those most likely to benefit while minimizing its use others thus limiting excess morbidity and mortality associated with serious hyperkalemia.

B. Study Design and Statistical Analysis

This study is designed as a iandormized, double blind, placebo controlled trial. The subjects will be randomized to receive Spironolactone 25 mg by mouth one time daily versus an identical looking placebo. The subject's serum aldosterone levels will be assessed upon enrollment. Patients' initial serum aldosterone levels will be used during the data analysis phase for dichotomization into two predefined groups - those with suppressed levels (below 15 ng/dl) and those without suppressed aldosterone (~: 15 ng/dl). Follow-up will be for 2 years. The primary outcome is a composite outcome of death from all cardiovascular events including MI, ventricular arrhythmia and progression of CHF from class III to IV. Additional outcomes of hospitalization for cardiac causes including ischemia and arrhythmia and a worsening of CHF class will also be included in the composite endpoint. The secondary endpoint of all-cause mortality will also be examined. Upon enrollment data regarding baseline left ventricular ejection fraction, blood pressure, history of arrhythmic event, smoking history, etiology of heart failure, baseline serum creatinine, baseline serum K and Na, age, sex, length of use of ACE inhibitors, ACE-inhibitor dose, use of digoxin, potassium supplementation and beta blockers will be collected as well for inclusion in the final analysis. Data on both the primary and secondary endpoints will be collected during brief interviews conducted when patients present for scheduled blood draws as well as by 3 month phone follow-up and via chart review at 12 months and 2 years.

The primary and secondary endpoints will be analyzed on an intention-to-treat basis and Kaplan Meier curves will be constructed for subjects in the treatment and placebo group based on their initial level of serum aldosterone. A Cox proportional-hazards regression model will be constructed to examine the relationship between base-line subject variables , initial serum aldosterone level (< 15 ng/dI or >_ 15 ng.dl) and response to Spironolactone. Continuous variables will be evaluated by Student's t-test and categorical variables will be evaluated by Chi-square analysis

The goal is to enroll 2800 subjects. This sample size was calculated based on the assumptions that 70% of the subjects will have low or suppressed serum aldosterone levels while 30% will have elevated, non-suppressed serum aldosterone levels[10]. In addition, it is assumed that there will be a 10% absolute reductionin the primary outcome for patients with elevated a1dosterone levels receiving Spironolactone compared to those with elevated a1dosterone levels who 2 are receiving placebo (from an incidence of 0.45 to 0.35) [2]. It is also assumed that there will be a 10% absolute reduction in events in patients with low serum aldosterone regardless of treatment group co ared to those in the placebo group 5 with elevated a1dosterone levels (0.45 to 0.35) [4,5]. The study is powered at 80 % to detect the above differences and a two-tailed cc is set at the level of 0.05. An independent data and safety monitoring board will monitor all available data at 3 month intervals.

C. Study Procedure

Upon enrollment patients will undergo a standard medical history and physical by one of the principle investigators/physicians. At the time of enrollment an initial aliquot of 10 cc of blood will be drawn for analysis of serum electrolytes, creatinine and serum aldosterone. Patients should expect minimal discomfort and minimal risk from this procedure. Phlebotomy will take place with the patient in the supine position, after 30 minutes at rest and between 8 am and noon. Additional phlebotomy for electrolyte analysis and analysis of serum creatinine will occur at 0, 4, 8, 12, 24, 36, 48, 72, 96 and 104 weeks. The anticipated duration of follow-up is 24 months from enrollment.

D. Study Drugs

Spironolactone, an aldosterone receptor antagonist (Searle) is an FDA approved drug with indications for use in CHF, as a treatment of hypertension, primary hyperadlosteronism, ascites and edema in the setting of cirrhosis, and 12 hypokalemia associated with diuretic use[12]. Spironolactone has been previously shown to provide survival benefit to patients with advance heart failure in combination with standard therapy but has also been associated with an increase [2,11] in fatal hyperkalemia . Therefore, it is now being studied to determine if there is a subset of patients with advanced heart failure and incomplete suppression of serum aldosterone despite maximal ACE-1 therapy who may preferentially benefit from its use. This would allow clinicians to limit its use to those expected to gain maximum benefit while reducing the incidence of adverse events. In this study the treatment group will be assigned to receive Spironolactone 25 mg by mouth daily vs. an identical appearing placebo. The study dose and the dose used in clinical practice are the same. Patients will not be allowed to be on potassium sparing diuretic for the duration of the study and potassium supplementation will be discouraged unless the serum potassium is less than 3.5 nimol/fiter. If serious hyperkalemia develops (K>= 6 mmol/liter) in any subjects the treatment dose will be decreased to 25 mg po QOD (placebo QOD) and then discontinued if hyperkalemia. persists.

Known side effects with the study drug include hyperkalemia, gynecomast ia and breast pain, as well as rare arrhythmia, ataxia, cough, diaphoresis, diarrhea, dizziness, drowsiness, dry mouth, dyspnea, dysuria, headache, agranulocytosis, anaphylaxis, hepatotoxicity, renal failure, nausea, GI upset, hirsuitism, sexual and menstrual irregularities, fever, rash, and metabolic acidosis.

E. Medical Device

No novel medical devices will be employed for use in this study.

F. Study Questionnaires

A basic medical history questionnaire currently in development and medical chart review investigating the study subjects past medical history including information regarding left ventricular ejection fraction, blood pressure, history of arrhythmic event, etiology of heart fidlure, baseline serum creatinine, baseline serum K and Na, age, sex, smoking history, length of use of ACE inhibitors, ACE-inhibitor dose, use of digoxin, potassium supplementation and beta blockers and allergies will be utilized at the time of enrolhnent.

G. Study Subjects

The goal of the current study is it to examine a group of patients analogous that studied in the FALES trial[2]. Therefore patients will be eligible for enrollment if they have New York Heart Association (NYHA) class IV heart failure in the six months prior to enrollment, or are NYHA III or IV at the time of enrollment. They must have received the diagnosis of CHF at least 6 weeks prior to enrollment. Additionally, it is required that subjects are on an ACE inhibitor, a loop diuretic and have a left ventricular ejection fraction of less than or equal to 35% as determined by cardiac echo or right hear catheterization within the 6 months prior to enrollment. Subjects are allowed to be receiving digitalis and vasodilator therapy but are not allowed to be receiving Spironolactone or other potassium-sparing diuretics or oral potassium supplements unless they have serum potassium of less than 3.5 mol per liter. Exclusion criteria include valvular heart disease that is amenable to operative repair, congenital heart disease, unstable angina or MI within the past 3 months, primary hepatic failure, active cancer, or other fife-threatening diseases apart from heart failure. Subjects will be excluded if they have a baseline serum creatinine of greater than 2.5 mg per deciliter and initial serum potassium of greater that 5 mmol per liter[2,11]. Patients awaiting or status-post orthotopic heart transplant will also be excluded from the study.

Additionally, patients must be deemed to be clinically stable with stable fluid balance without evidence of edema, fluctuating body weight and stable renal and pulnionary function as determined during the physical exam conducted at the time of enrollment..

H. Recruitment of Subjects

Potential subjects will be identified by their primary care givers in the setting of the academic medical center's outpatient clinic and inpatient medical service. Additional subjects will be recruited from the academic medical centers' cardiology clinic. The patient's primary physician will determine if the patient is suitable for inclusion in the study and will have an initial discussion regarding potential enrollment in the study including the risks and benefits of participation as well. If the patient is amenable to inclusion in the study they will be referred to the research team for full consent, and enrollment including initial physical exam, medical history and phlebotomy.

I. Confidentiality of Study Design

All subjects will be assigned a unique subject code that does not include any personal identifier (including hospital unit number, social security number, subject initial, phone number, addresses) or other information that could be used to identify the subject's identity. All subjects will have a unique code number assigned to them and all data will be recorded by code number and will be accessible to only study investigators. All subjects, investigators and clinicians will be blinded as to study treatment group.

J. Conflicts of Interest

None of the investigators have any conflict of interest relating to this study.

K. Location of the Study

This study will be conducted at Columbia Presbyterian Medical Center as well as at other academic medical centers yet to be identified. Activities of the study will be conducted within clinical areas under the auspices of the department of Medicine. Approval for the study from -the chairman of the department of medicine will be sought prior to initiation of the study. Other clinical sites will receive approval of the appropriate departmental chairman and IRB prior to initiation of study activities at those sites.

L. Potential Risks

Potential risks for patients receiving the study drug, Spironolactone, include serious and potentially fatal hyperkalemia as well as breast pain and gynecomastia. The risk of hyperkalemia will be minimized by excluding patients with renal insufficiency (creatinine $\geq$ 2.5 mg/d1) or hyperkalemia (>5 mmol/1) at baseline, by frequent monitoring of serum electrolytes and by limitingthe use of potassium supplementation. Patients receiving the placebo are a risk for worsening of their CHF. Additional minimal risk comes from the phlebotomy procedure performed periodically throughout the study period. This risk includes bleeding and infection at the. venous puncture site. An independent data safety monitoring board will review all available data at 3 month intervals and all adverse events (hyperkalemia or any other unanticipated event) will be reported to both the data safety monitoring board and the GCRC. The study will be terminated early if the incidence of hospitalization for hyperkalemia increases in the Spironolactone group by more than 511000 or if there is an increase in hyperkalemia associated mortality of 1.5 per 1000[10]

M. Potential Benefits

Subjects receiving the study drug may expect a decrease in their cardiovascular morbidity and mortality including fewer cardiac events, myocardial infarctions arrhythmias, fewer hospitalizations for worsening of their heart failure and fewer deaths. Long term benefits to society include limiting the use of a drug with potentially serious and fatal side-effects to those patients who benefit most from its use.

N. Alternative Therapies

The groups in this study will be receiving the standard of care for advance heart failure plus an additional aldosterone receptor antagonist in the treatment group. None of the therapies employed in this study are considered experimental.

O. Compensation to Subjects

There will be no monetary compensation given for participation in this study.

P. Costs to Subjects

Subjects will incur no monetary costs by participation in the study.

Q. Minors as Research Subjects

No minors will be enrolled as part of this

R. Radiation or Radioactive Substances

Subjects will not be subjected to radiation or radioactive substances as part of this study protocol.

S. References

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