A. Study Purpose and Rationale

Background

Congestive heart failure (CHF) affects roughly 6 million people in the United States with incidence rates rising steadily. Of even more concern, however, is the high percentage of patients seeking re-admission within 6 months of treatment and the average duration of hospitalization which normally range from 5-10 days[1]. The annual cost of CHF readmissions is estimated to be $12 billion annually and the average hospital loses roughly $1300 for each patient admitted for acute decompensated heart failure[2].

Loop diuretics have been the cornerstone of treatment for reducing symptoms of volume overload, which is the predominant reason for CHF readmissions. All of the loop diuretics work on the sodium-potassium-chloride transporter of the thick ascending limb of the loop of Henle leading to decreased reabsorption of water with other ions. There are 4 loop diuretics available in the US – furosemide, bumetanide, torsemide, and ethacrynic acid – and despite the fact there is little to no data supporting furosemide as superior, it is the most commonly prescribed diuretic in managing CHF volume status long term. In fact, it ranked number 17 in a list of most prescribed drugs in 2008 and was the only loop diuretic to be in the top 200[3]. Furosemide was introduced into the market in 1966, whereas bumetanide and torsemide were made available in 1983 and 1993, respectively. As a result of the large gap in time, furosemide was available as a significantly less expensive generic drug for years before its competitors. Today, a 30 day supply of furosemide costs $4 and a 30 day supply of torsemide costs roughly $15-$20.

Review of literature

Though torsemide is the more expensive drug, it has a superior pharmacokinetic profile. The bioavailability of furosemide is only about 50% overall with significant interpatient and intrapatient variability (range of 10-100%) and an absorption that is affected by consumption of food. Torsemide however is more predictably absorbed with bioavailability of 80-100%, a longer half-life (3-4 vs. 1.5-2), and an absorption profile that is not affected by food.[4] This longer half-life is important, as shorter half life diuretics can cause “rebound” periods where subtherapeutic concentrations in the body lead to sudden increase in sodium avidity by the kidney.

In addition to superior pharmacokinetics, torsemide may exhibit a superior pharmacologic effects. In two studies of rats, torsemide was shown to inhibit the renin-angiotensin-aldosterone system by inhibiting the effects of aldosterone[5]. Spironolactone, which was shown to improve mortality in CHF patients in NYHA class IV, has the same mechanism. Finally, the effects of loop diuretics on myocardial fibrosis was examined in a randomized, open-label, parallel-group study of 36 patients. They measured indexes of collagen type I synthesis and degradation as well as performed endomyocardial biopsies in patients receiving either furosemide or torsemide. The theory was that myocardial accumulation of collagen fibers reduces LV function and given that increased aldosterone leads to synthesis of collagen fibroblasts, some aldosterone blockade might lead to significant differences in fibrosis with torasamide vs. furosemide. They found a significant improvement in all measured indicators of fibrosis among patients receiving torsemide, but not furosemide[6].

There have also been some clinical studies that suggest positive outcomes with torsemide versus furosemide. The Torsemide in Congestive Heart Failure (TORIC) study was an designed to investigate the safety, tolerability, and efficacy of torsemide in CHF patients compared to furosemide and other diuretics. Although it was not powered to detect mortality differences and furosemide was grouped with other diuretics, they did find significantly lower mortality in the torsemide group vs the other group (n=17, 2.2% vs. n=27, 4.5%)[7]. An open-label, randomized trial of torsemide compared with furosemide therapy in CHF patients was performed for 234 patients for 1 year with the primary endpoint being readmission to the hospital for heart failure. This group found that the torsemide group were significantly less likely to require readmission for heart failure (17% vs. 32%) and that group also had less hospital days for heart failure (106 vs. 296 days)[8].

Based on the pharmacokinetic profile and possible aldosterone antagonism, torsemide appears to be a better first line treatment for CHF diuresis. There have been several studies that suggest that, however none of them masked, and there is also little to no data supporting furosemide over torsemide. Though torsemide is a more expensive drug, if the risk of readmission for acute decompensated heart failure can be shown to be significantly reduced, then it can be viewed as cost effective when taking into account the costs of hospitalization and potential complications.

B. Study Design and Statistical Analysis

Hypothesis

The rate of readmission for congestive heart failure will be significantly reduced in patients using torsemide as a loop diuretic instead of furosemide.

Study overview

This will be a prospective, randomized, double-masked, flexible dose trial which will investigate the comparative efficacy of torsemide vs furosemide. The primary objective is to assess percentage of patients having a single readmission for acute decompensated heart failure in the two groups. A secondary outcome will be to calculate a cumulative symptom score assessed at various time points.

Study design

Patients presenting to the New York Presbyterian hospital for acute decompensated heart failure on furosemide as their only prescribed diuretic will be eligible to enroll. The patients will randomized on discharge from the hospital to continue therapy with furosemide or be switched to torsemide. The torsemide arm will receive $1/4^{th}$ the dose of furosemide as the drug is 4 times as potent in order to equilibrate the therapies. Inclusion criteria will be evidence of systolic dysfunction on reported echocardiograph (LVEF < 40%), NYHA class or II or III, age > 18, and currently taking furosemide. Exclusion criteria will be history of adverse effects from torsemide.

Once a patient is found to be eligible and signs the informed consent, a random number generator will determine which arm the patient will be randomized to. Only the study coordinator will have access to this information. The study medications will be packaged in

quick dissolving capsules using a double-dummy technique such that each capsule contains the active form of one drug and the inactive form of the equivalent dose of the other (containing active 5mg torsemide or 20 mg furosemide and matching placebo).

The patient will return to his primary physician for scheduled visits at 1, 3, 6, 9, and 12 months. The patient's physician will be given a detailed sheet explaining the dose conversion between the two drugs. The physician will know the dose the patient's medication in relative terms (i.e. 10 mg torsemide or 40 mg furosemide) but will not know that actual identity. The physician can adjust the dose based on clinical signs and symptoms using a conversion scale which matches each pill to its equivalent dose in furosemide/torsemide. However, should the primary physician find the volume status of the patient too tenuous to manage in this way, they may promptly remove the patient from the trial. During these clinic visits, major symptoms of CHF including dyspnea, orthopnea, edema, and exercise tolerance will be rated on a scale of 0 (absent) to 3 (severe).

Readmission for heart failure is an endpoint but will be considered a failure of therapy and the patient's medication will be unmasked at this point for both them and their physician. If the patient is readmitted, the date will be recorded so that a time to readmission Kaplan-Meir curve could be constructed

Statistical analysis

Collected data from the American Heart Association's Quality of Care & Outcomes Research shows readmission rates for heart failure between 10 and 32%. The study of Murray et. al which looked at readmission rates for ADHF for patients on torsemide vs. furosemide were 17% vs 32%, though this was looking at a relatively small group of 234 patients. Given the prevalence data and the perception that not a large difference in hospital readmission would be required for adequate treatment effect, a power calculation at goal of 80% was used via chi-square test estimating readmission rates of 20% and 30% in the torsemide and furosemide arms. This calculation yielded a total of 318 patients required for each group with a total recruitment goal of 636 patients. Cox proportional hazard modeling will be performed to judge the possible results based on possible covariates such as number of previous hospitalizations before the trial, age, and ejection fraction.

In addition to the primary outcome of hospital readmission, the symptom score will also be measured at each clinic follow up time point and the progression/regression will be mapped to time. Also, Kaplan-Meier curve will show time to readmission for the two therapeutic arms.

C. Study Procedure

No procedures will be performed on the patients as part of this study. The duration of the study will be one year for each enrolled patient. If we can recruit 150 patients per year the length of the entire trial will likely be around 5 years.

D. Study Drugs

The drugs used in the trial are torsemide and furosemide. Both are approved for the use of diuresis in congestive heart failure. Rationale for the drugs being used are explained in the introduction. There are three major types of side effects related to loop diuretic use: general diuresis side effects (including electrolyte abnormalities), hypersensitivity reactions, and ototoxicity. Since the patients randomized to the furosemide arm were already on the drug, there are no issues with that group. The side effect profile of torsemide is essentially the same since they are both sulfa based loop diuretics so there should be no issue with switching to a drug in the same class. The dosage regimen was explained in the study design.

E. Medical Device

Not applicable

F. Study Questionnaires

At each clinic follow-up, the patient will answer a series of questions related to their symptom burden including dyspnea, edema, orthopnea, and exercise tolerance.

G. Study Subjects

Inclusion criteria will be evidence of systolic dysfunction on reported echocardiograph (LVEF < 40%), NYHA class or II or III, and age > 18. Exclusion criteria will be history of adverse effects from torsemide.

H. Recruitment of Subjects

Subjects admitted to the New York Presbyterian hospital who meet the inclusion criteria will be identified and approached about enrollment before they are discharged. In addition, we will attempt to contact their primary physician to let them know about the trial

I. Confidentiality of Study Data

All study data will be stored in a secure location and coded such that personal identifiers will not be used as coding mechanisms.

J. Potential Conflict of Interest

There is no potential conflict of interest

K. Location of the Study

The study will be located in the two primary CPMC sites – the Millstein Hospital and the Allen Pavillion

L. Potential Risks

The primary risk is a decreased ability to optimally manage volume in patients when the physician is masked to the identity of the diuretic. As a result, the patient's condition may worsen if the physician feels uncomfortable in titrating up a masked medication. Fortunately, there's essentially a direct dose relationship between the two drugs so management should be similar. Additionally, the patient may be withdrawn from the trial at any point if it is felt that their volume status is too tenuous.

M. Potential Benefits

Potential benefits exist for the patient who may have a decreased risk of hospitalization if using a diuretic that is more effective. There also potential benefits to the entire health care system which would save money if CHF readmission rates were reduced on a large scale.

N. Alternative Therapies

Not applicable

O. Compensation to Subjects

In exchange for participating in the study, the patient will have their diuretics paid for by CUMC. The amount varies depending on the dose, but for the average patient in the furosemide arm that would mean ~$50-60 per year and for the average patient in the torsemide that would be ~$240 per year.

P. Costs to Subjects

There will be no additional costs to the patient

Q. Minors as Research Subjects

Not applicable

R. Radiation or Radioactive Substances – not applicable

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