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Project Title: A comparison of hydrochlorothiazide and metolazone in combination with furosemide in congestive heart failure patients.

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HRRC Protocol #: 02-276

A. SPECIFIC AIMS – HYPOTHESIS:

Null-Hypothesis:

This research will test the following null-hypothesis:

The diuretic combination of furosemide-metolazone is equivalent to furosemide-hydrochlorothiazide in promoting diuresis for patients with congestive heart failure.

Objective:

To establish if there is a difference between furosemide-metolazone versus furosemide-hydrochlorothiazide in promoting diuresis in patients with congestive heart failure.

Secondary Objectives:

To determine the duration of action of furosemide as monotherapy and in combination with either hydrochlorothiazide or metolazone.

To determine the effect of diuretic combination therapy on neurohormonal activation.

To determine the relative influence of metolazone and hydrochlorothiazide on parameters predicting ventricular arrhythmias.

B. BACKGROUND AND SIGNIFICANCE:

Diuretics serve as a primary pharmacological treatment of congestive heart failure with acute or chronic fluid overload. Loop diuretics, such as furosemide, are the most effective agents in producing diuresis. These agents act to inhibit the sodium/chloride cotransport in the ascending limb of the loop of Henle, where 25% of the filtered load of sodium is reabsorbed. [1,2,3,4,5] Thiazide diuretics, such as hydrochlorothiazide, act at the distal convoluted tubule to inhibit sodium and chloride reabsorption. These diuretics are comparatively less potent versus the loop diuretics for the reason that only 5%-10% of the filtered load of sodium is reabsorbed in the distal convoluted tubule.[1,2,3,5] Metolazone, a quinazoline diuretic, has similar pharmacologic characteristics as the thiazides. It acts primarily to inhibit sodium reabsorption at the distal convoluted tubule and to a lesser extent at the proximal convoluted tubule. [1,2,3,5,6]

Diuretic resistance occurs when a potent diuretic drug, such as furosemide, is given in therapeutic doses and fails to reduce extracellular fluid volume to the desired level in an edematous patient.[2,3,5,6] Diuretic resistance can simply occur as a result of excessive salt intake, patient noncompliance, or drug-induced

resistance. Other forms of resistance include acute adaptation, postdiuretic retention, and chronic adaptation.

Acute adaptation limits the utility of single diuretic therapy by increasing the ability of the kidneys to reabsorb sodium chloride (NaCl). When a loop diuretic is administered, it acts on the thick ascending limb of the loop of Henle where it blocks the sodium reabsorbing capacity. Consequently, more sodium is delivered to the distal parts of the nephron. Since the NaCl transport system in the distal convoluted tubule is unsaturated and load dependent, this increased NaCl delivery leads to increased NaCl reabsorption. [2,3,4,5,7] This mechanism of acute adaptation can be prevented by the addition of a diuretic that acts on the distal convoluted tubule such as metolazone or hydrochlorothiazide, to block this increased reabsorption.

Postdiuretic retention is an adaptive response in which there is a decrease in response to a diuretic after the first dose has been administered. As a result of the short half-lives of loop diuretics, for example furosemide has a half-life of 0.5-1.1 hours, the plasma drug concentration usually falls below therapeutic concentrations before the next dose of the diuretic is administered.[8] During this time the nephron undergoes rebound sodium retention and reabsorbs large amounts of sodium, which may nullify the prior natriuresis. Since this rebound sodium retention is thought to be mediated by increased sodium reabsorption in the distal convoluted tubule, it may be prevented by the administration of an additional diuretic, which inhibits transport in this segment.[2,3,4,5,9] The added drug should preferably have a half-life greater than the loop diuretic. [3] Two possible choices are hydrochlorothiazide and metolazone which both have longer half-lives, 5.6-14.8 hours and 6-20 hours respectively, and act to inhibit sodium reabsorption in the distal convoluted tubule.[8]

With chronic administration of a loop diuretic, the constant increase in the concentration of solute that escapes from the loop of Henle floods the more distal regions of the nephron. These cells undergo structural and functional adaptive processes such as increasing the number of membrane Na+-K+-ATPase pumps. The increase in Na+-K+-ATPase pumps leads to an increased transport capacity of the distal nephron. This adaptation is activated by the necessity for increased cellular reabsorption, which leads to a decrease in overall diuresis and seems to be an important cause of diuretic resistance. Diuretics such as metolazone and hydrochlorothiazide that block the distal regions in the nephron would act to block this adaptation and increase diuresis. [2,3,4,5,6,7]

Studies have shown that metolazone and hydrochlorothiazide have demonstrated a synergistic response when used in combination with furosemide in congestive heart failure patients. A study conducted by Grosskopf and colleagues demonstrated that the combination of furosemide and metolazone induced greater natriuresis, urinary output, and weight loss compared with those produced by furosemide or metolazone alone.[10] The study included ten severe congestive heart failure patients, six females and four males, with a mean age of 67 years. On the first day, the patients received an I.V. dose of 120 mg of

furosemide. The mean 24-hour urine volume was 1810 ± 397.4 mL and the mean body weight was found to be 53.4 ± 9.3 kg. After the addition of 5 mg of oral metolazone, the 24-hour urine volume was found to be 2470 ± 608.8 mL and the mean body weight was 51.2 ± 9.0 kg ($P < 0.05$).

In addition, a study performed by Dormans and Gerlag showed that the addition of hydrochlorothiazide with furosemide had a synergistic effect and resulted in decreased body weight, increased urine volume, and increased fractional sodium excretion.[7] This study included twenty patients with severe congestive heart failure, six females and fourteen males, with a mean age of 70.8 years and a proven diuretic resistance to furosemide (daily dose greater than 250mg). These patients were given hydrochlorothiazide (25-100 mg orally) in combination with furosemide. This combination led to a mean reduction in body weight of 6.7 ± 3.3 kg per patient. Mean daily urine volume increased from 1899 ± 958 ml to 3065 ± 925 ml ($P< 0.001$) and fractional sodium excretion increased from 3.5 ± 3.2% to 11.5 ± 9.0% ($P<0.001$).

Restricting dietary sodium intake and administering a single diuretic drug will lead to clinical improvement in the majority of congestive heart failure patients. However, some patients with congestive heart failure even when given therapy with high-dose furosemide still have edema. A major problem results when furosemide and a restricted diet fail to reduce the extracellular volume to the desired level. The extreme fluid retention that results, if left untreated, may result in hospitalization. Loop diuretics have similar pharmacologic characteristics; therefore, administering another loop diuretic is not a valid option.[2,8] As a result, diuretics with different mechanisms of action should be utilized.[1,7] Studies show that the combination of metolazone-furosemide act synergistically to induce greater urinary output and weight loss.[10,11,12,13] In addition, the combination of hydrochlorothiazide-furosemide also act synergistically to induce increased diuresis.[7] The current guidelines for treating diuretic resistance in congestive heart failure patients recommend the metolazone-furosemide combination.[14] However, there is no evidence to conclude that this combination is superior to hydrochlorothiazide-furosemide in increasing diuresis.

Sudden death is predominantly caused by ventricular arrhythmias (tachycardia or fibrillation). The interplay of a cardiac substrate for ventricular instability such as infarction or dysfunction with dilation and autonomic and electrolyte factors is central to the triggering of these arrhythmias. The electrolyte and fluid shifts produced during diuresis may place patients with the substrate for ventricular arrhythmias at further risk due to the loss of potassium and magnesium. Monitoring of the patient's rhythm by telemetry can aid in evaluating patients undergoing diuresis. Evaluation of electrocardiographic parameters on the surface electrocardiogram including QRS and QT dispersion can predict the risk of ventricular instability in a patient undergoing physiologic changes such as diuresis.[15,16]

Activation of the neurohormonal system in response to heart failure serves as an initial adaptive mechanism but over time becomes maladaptive impairing the

function of the heart, vasculature, and kidneys. Sympathetic activation has been demonstrated to be arrhythmogenic.[17] Increases in angiotensin II are deleterious in heart failure due to vasoconstriction, promotion of proximal renal tubule sodium reabsorption, and stimulates the release of additional neurohormones such as endothelin, aldosterone, vasopressin, and cytokines. In addition, angiotensin II and high concentrations of aldosterone augment sympathetic activation.[18,19] By reducing volume, diuretics reflexively increase the concentrations of renin, and thus angiotensin II and aldosterone.[20,21] The natriuretic peptides, atrial and brain natriuretic peptide (ANP and BNP), act in opposition to the renin-angiotensin-aldosterone system.[22] These peptides act to dilate renal blood vessels, decrease renin and aldosterone secretion, and decrease sodium reabsorption in the collecting duct. ANP and BNP are respectively synthesized in the atria and ventricle of the heart. BNP, also known as B-type natriuretic peptide, concentrations are normally much lower than ANP concentrations. However in CHF patients plasma BNP levels increase progressively more than ANP values and have been used to provide diagnostic and prognostic information.[22-24] Therefore, the current study will measure concentrations of these neurohormones and determine the effects of combination diuretic therapy on these parameters.

The purpose of this study is to compare the diuretic efficacy of the combination of furosemide-metolazone with furosemide-hydrochlorothiazide in patients with congestive heart failure. The primary objective is to establish which combination is the most effective in promoting diuresis in congestive heart failure patients. The effects of both regimens on electrocardiographic parameters of ventricular instability and neurohormonal parameters will also be assessed as secondary objectives.

C. PRELIMINARY STUDIES:

To the best of our knowledge, there have been no studies comparing the efficacy of the two diuretic combinations.

D. RESEARCH DESIGN AND METHODS:

Study Design:

This will be a randomized, double-blind, crossover study designed to compare the efficacy of hydrochlorothiazide and metolazone in combination with stable doses of furosemide in congestive heart failure patients.

The specific dose of hydrochlorothiazide will be determined by the individual's creatinine clearance. A creatinine clearance of 30-50 mL/min will indicate a dose of 50 mg per day. A creatinine clearance of > 50 mL/min will indicate a dose of 25 mg per day.[5] If metolazone is added to their regimen, the specific dose will be determined using the equivalence ratio of 5 mg metolazone to 50 mg hydrochlorothiazide.[8]

Twenty-six subjects will be studied. They will be recruited from the University of New Mexico Congestive Heart Failure Clinic.

Inclusion criteria:

- Age >18 years
- Diagnosis of chronic congestive heart failure with an ejection fraction ≤45%
- Currently on a stable regimen of furosemide consisting of a daily dose of ≥80 mg for at least two weeks.
- Patients receiving ACE-inhibitors and/or beta-blockers must be taking these medications for at least two weeks in stable doses.

Exclusion criteria:

- Renal dysfunction (serum creatinine >2 mg/dl or creatinine clearance of <30 ml/min as calculated by the Cockroft and Gault equation)[25]
- Hepatic dysfunction (AST and ALT >3 times the upper limit of the normal)
- Hypokalemia (<4.0 mg/dl)
- Concomitant treatment with any diuretic other than furosemide (with the exception of spironolactone).
- Gout
- Lupus erythematosus

Study procedures:

Study procedures will be performed at the University of New Mexico General Clinical Research Center.

After obtaining written informed consent, patients will be randomly assigned to one of two groups. Both groups will be admitted to the hospital for a period of four days (five nights) on two separate occasions. Daily sodium intake will be restricted to less than three grams per day, and fluid intake to less than three liters per day. For the first twenty-four hours of each admission, both groups will continue their regular medication regimen to establish a baseline for the measured variables. For the remaining three days, the patients will have either hydrochlorothiazide or metolazone added to their daily regimen of furosemide. Blinding and randomization will be maintained by the UNMH research pharmacist (Nancy Morgan, R.Ph.). The dose of the additional drug will be administered one hour prior to the dose of furosemide to ensure adequate absorption. After the initial four-day hospitalization, the patients will undergo a washout period of one week where they will be sent home and continue on their regular medication regimen. When the patients return for the next four-day period they will be treated with the alternate drug. Patients will be asked to maintain a consistent

dietary intake (sodium, potassium, etc.) and drug therapy throughout the study, i.e. potassium supplements and drugs that promote sodium retention (NSAIDS, etc.). Starting 3 days prior to each admission, the patients will be required to eat only the food provided by the UNM General Clinical Research Center. The foods provided will be consistent with the dietary sodium and fluid limitations.

Study Variables:

Hemodynamic measures: During each admission, the patients' blood pressure and pulse will be measured every hour for the first six hours, every two hours for the next six hours, and then every four hours for the remainder of the twenty-four hours on days one and two. On days three and four, the patients' blood pressure and pulse will be taken every six hours. Weight will be measured at baseline, two hours, six hours, twelve hours, and twenty-four hours on days one and two. On days three and four weight be will be taken once daily in the morning.

Renal, electrolyte, and endocrine parameters: Twenty-four hour urine will be collected daily. Urinary output will be quantified at 2 hours, 6 hours, 12 hours, and 24 hours on days one, two, and four and at 24 hours on day 3. In addition we will measure the following urinary variables: potassium, sodium, creatinine, aldosterone, and protein. On days one, two, and four, blood samples will be taken at baseline, 2 hours, 6 hours, 12 hours and 24 hours after the dose of diuretic(s) to determine changes in serum sodium, potassium, chloride, bicarbonate, uric acid, creatinine, magnesium, blood urea nitrogen. In addition blood samples will be taken on the same days and times to determine changes in: catecholamines, angiotensin II, plasma renin, aldosterone, and brain natriuretic peptide. On day three blood will be obtained 6 hours post diuretics to monitor serum electrolytes as a safety precaution.

Measures of ventricular instability: A standard 12-lead electrocardiogram (ECG) will be performed at the following times: time 0, 2 hours, 6 hours, and 12 hours post-dose. The QT and QRS intervals will be measured on all ECG's. QRS dispersion and QT dispersion will be calculated on all ECG's and defined as the maximum difference in the QRS and QT intervals.

Statistical Analysis:

The main analysis will be repeated measures ANOVA with day (comparison to baseline) and added drug (due to crossover) as repeated factors. Post-hoc testing will be done using paired t-tests.

The sample size was calculated based on the primary outcome variable, the mean difference in 24-hour urinary output in milliliters (mL). For simple and robust power analysis, the paired t-test that compares 24-hour urinary output on day 3 with each added drug was used. We determined a mean difference in change from baseline in 24-hour urinary output of 300 ml between the furosemide-metolazone and furosemide-hydrochlorothiazide regimens to be

clinically significant. Previous studies with furosemide and hydrochlorothiazide and furosemide and metolazone demonstrated mean 24-hour urinary outputs ± s.d. of 1899 ± 958 ml and 1810 ± 397 ml at baseline with furosemide monotherapy and 3065 ± 925 ml and 2470 ± 608 ml with combination therapy, respectively.[7,10] Using these data and assuming moderate correlations within subject due to the baseline-controlled crossover design is 0.7, a sample size of 20 patients is adequate to detect the 300 ml difference with 80% power at a 5% level of significance. This is reasonable since comparison of the two referenced studies found a difference in the change from baseline of 506 ml.[7,10] Accounting for a 25% dropout rate, 26 subjects will be enrolled in the study.

All statistical analysis will be performed using SAS v6.12.

Potential assumptions and limitations:

A major limitation to the study is that patients included in the study are clinically stable and therefore the results may not be generalizable to decompensated CHF patients. For the purposes of our study we are assuming that the patients will remain on the same drug therapy, as well as sodium and fluid intake throughout the study, so as not to introduce any additional variables. We are also assuming that the dose of metolazone given to the patients is equivalent to the dose of hydrochlorothiazide. The fact that there is no way of determining an exact equivalent dosage limits our study. Another limitation is the fact that our patients will only be receiving the additional drug and being monitored for 4 days. The study drugs may not have enough time to reach maximal effect. Therefore in practice, where the drug may be given over a greater period of time, diuresis and adverse effects may be more pronounced.

E. HUMAN SUBJECTS:

1. Gender and minority inclusion:

This study will enroll 26 patients with the diagnosis of congestive heart failure over 18 years of age. This project will involve subjects of race and gender commensurate with the general population of Albuquerque, NM and the population seen in the University Hospital Congestive Heart Failure Clinic. The population of Albuquerque, NM is approximately 40% Hispanic and 50% female and our subject enrollment should reflect this.

	African American	Hispanic	Asian	American Indian	Caucasian	Other	Total
Female	1	6	0	0	6	0	13
Male	1	6	0	1	5	0	13

Total	2	12	0	1	11	0	26

2. Sources of research material:

Each subject will have about 13 tablespoonfuls of blood taken over the duration of the study. This will amount to about 400 mL of blood withdrawn from each subject for the entire study. All blood samples will be used solely for research purposes. Each subject will have their urine collected for the entire 8-day admission period.

3. Plans for recruitment:

Recruitment of subjects will involve personal contact in the University Hospital Congestive Heart Failure Clinic and from the UNMH Adult Cardiology Inpatient service. Informed consent will be obtained from each subject prior to the initiation of study procedures by study personnel. The consent form to be used in this study is attached to this proposal as Appendix A.

4. Potential risks:

Subjects involved with this study may experience hypokalemia, dizziness, headache, and muscle cramps. These side effects occur in less than 10% of patients.[8] Other potential side effects include hyperglycemia, sun sensitivity, hypotension, nausea and vomiting which have been reported to occur in less than 1% of patients.[8] There is also a slight risk associated with the blood draws, including possible infections at injection sites, and pain upon needle insertion. The subjects due to the diuresis and possible potassium and magnesium depletion may be at higher risk for ventricular arrhythmias.

5. Procedures for protecting against/minimizing risks:

The 3-day treatment regimen selected should minimize any adverse effects associated with this study. In addition, serum electrolytes will be monitored frequently and potassium and magnesium supplementation will be provided if necessary. If symptomatic hypotension develops, the next dose of study drug will be withheld. The risks involved with blood draws will be minimized by having all blood samples drawn by experienced GCRC nursing personnel. The subjects will be monitored for potential ventricular arrhythmias during the study by performing standard 12-lead electrocardiogram (ECG) at the following times: time 0, 2 hours, 6 hours, and 12 hours post-dose. This is probably an advantage over the usual outpatient management of these subjects, which would have no monitoring of their heart rhythm.

6. Clinical benefit to subjects:

Although subjects are unlikely to benefit directly from this research, their participation may lead to information that could help direct the therapy of individuals with congestive heart failure requiring combination diuretic therapy. The risk:benefit ratio of this study is fairly low.

F. JUSTIFICATION FOR UTILIZATION OF GCRC:

The use of GCRC resources is important for the success of this study. This is an investigator-initiated clinical project operating on very limited outside resources. Patients are not acutely ill, and cannot therefore be housed elsewhere in the hospital. The expertise of the GCRC nursing staff is needed to perform blood draws, collect urine, obtain electrocardiographic data, and vital signs all of which are integral for the success of the study.

G. REFERENCES:

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H. SUPPORT:

This project is currently receiving support from the University of New Mexico Health Sciences Center Research Allocation Committee Award. $7,150.00 .

I. GCRC NEEDS:

Please see attachments I-V.

J. INFORMED CONSENT:

Please see attached consent form which is currently under review by the Human Research Review Committee of the University of New Mexico (Appendix A).

K. BIOGRAPHICAL SKETCHES:

Please see Appendix B.

L. SUMMARY-ABSTRACT:

Objective: To establish which combination of diuretics is the most effective in promoting diuresis in congestive heart failure patients. Secondary Objectives: To determine the duration of action of furosemide as monotherapy and in combination with either hydrochlorothiazide or metolazone. To determine the effect of diuretic combination therapy on neurohormonal activation. **Background:** Diuretic resistance occurs when a potent diuretic drug, such as furosemide, is given in therapeutic doses and fails to reduce extracellular fluid volume to the desired level in an edematous patient. Studies have shown that metolazone and hydrochlorothiazide have demonstrated a synergistic response when used in combination with furosemide in congestive heart failure patients. The current guidelines for treating diuretic resistance in congestive heart failure patients recommend the metolazone-furosemide combination. However, there is no evidence to conclude that this combination is superior to hydrochlorothiazide-furosemide in increasing diuresis. **Methods:** Randomized, double-blind, crossover study to compare the efficacy of hydrochlorothiazide and metolazone in combination with stable doses of furosemide in 26 patients with congestive heart failure. The primary endpoint will be change in urinary output. Secondary endpoints will be changes in weight, neurohormones (angiotensin II, catecholamines, brain natriuretic peptide, aldosterone), and electrocardiographic parameters of ventricular instability. Study procedures will be performed at the UNM General Clinical Research Center. Patients will be hospitalized for 2 separate 4-day admissions, separated by a 1-week washout period. At each

admission each patient will receive furosemide in combination with either metolazone or hydrochlorothiazide (metolazone for one admission and hydrochlorothiazide for the other). Following administration of combination therapy, blood and urine samples will be collected throughout the day to chart the onset and magnitude of effect of each treatment regimen. Various hemodynamic, renal, endocrine, and neurohormonal parameters will be assesed as will the effect of each combination treatment on ventricular instability using 12-lead electrocardiography. Data will be analyzed using ANOVA to compare changes from baseline and the Student t-test to analyze intertreatment differences. All statistical analysis will be performed using SAS v6.12.

Consent form

HRRC letter of submission