

Vasopressin in Diuretic Refractory Heart Failure

R. John Crew

A. Statement of Study Purpose and Rationale Summary

Congestive heart failure is a common reason for admission to CPMC. Depressed cardiac function has many causes - from cardiovascular disease to viral myocarditis to chemotherapy induced heart failure. Acute exacerbations of CHF have even more diverse causes, but the mainstay of treatment is similar. Routine admissions often require intravenous diuretic therapy. Those who do not respond to diuretics may require inotropic support, often with milrinone, dobutamine, or both. The increased inotropy results in improved cardiac output, hopefully leading to improved diuresis. There is a subset of patients in whom diuretic therapy plus inotropic support are not enough to remove the excess extracellular fluid. They remain hospitalized for prolonged periods of time, uncomfortably edematous, frequently suffering complications of intravenous access, such as infection. There are few other therapies, short of heart transplant or continuous venous-venous hemofiltration, that can help these patients.

a. Vasopressin in Blood Pressure Regulation

Vasopressin is a natural hormone secreted by the posterior pituitary in response to increased plasma osmolarity and effective hypovolemia. It works via V1 receptors to increase vascular smooth muscle tone (thus modulating blood pressure) and via V2 receptors in the kidney to increase reabsorption of free water. It is unique as a pressor in humans. In normal volunteers, vasopressin infusion at physiologic doses does not significantly affect blood pressure.¹ Certain people are exquisitely sensitive to vasopressin's effects, particularly those with vasodilatory shock. It has recently become critical in the treatment of both septic shock and end stage hemorrhagic shock.^{2,3} Both instances appear to be vasopressin depleted states. Hormone infusion returns these patients to a more physiologic state. Vasopressin also appears to inhibit the vasodilation mediated by inflammatory cytokines. In vitro, vasopressin's binding to the V1 receptor inhibits the formation of nitric oxide and cGMP normally induced-by inflammation. It may have separate effects on vascular tone via modulation of the ATP sensitive K-channel.^{4,5}

b. Vasopressin in Heart Failure

Heart failure is a state of effective intravascular volume depletion, physiologically stimulating vasopressin secretion. Vasopressin levels are elevated above normal controls in these patients.⁶ Despite this, the systemic vascular resistance of heart failure patients is lower than would be expected (i.e. these patients are not maximally vasoconstricted). Common inotropic drugs used in the treatment of heart failure (milrinone and dobutamine) work by separate mechanisms to increase intracellular cAMP and cGMP. Cardiac output improves via two mechanisms -1) contractility is increased, 2) systemic vascular resistance decreases through non-specific peripheral vasodilation.⁸ Infusion of vasopressin in CHF patients off other all medications result in an increase in the systemic vascular resistance and a smaller decrement in cardiac output.⁷ *In vitro*, vasopressin inhibits the formation of cAMP by dobutamine, and in vivo reverses the hypotension induced by milrinone administration.^{9,10} Vasopressin inhibits this peripheral vasodilation, with only small decreases in cardiac contractility (in isolated rat heart, low doses of vasopressin actually increase heart contractility).¹¹ The kidney is effected differently by vasopressin. The efferent arteriole is preferentially constricted, increasing intraglomerular filtration pressure.¹² The increase in peripheral vascular resistance and blood pressure may increase renal blood flow; the increased efferent arteriolar tone combined with an increased pressure head could increase urine formation.

Two recently published studies showed the effectiveness of low-dose vasopressin in severe heart failure.¹³ These studies included sicker patients than those anticipated in this study; however, both showed statistically significant increases in urine output in patients on inotropic support.

B. Study Design and Statistical analysis

The study will attempt to answer three questions:

1. Does adding vasopressin improve urine output in diuretic refractory heart failure patients?
2. Does adding vasopressin improve the rate of weight loss in diuretic refractory heart failure patients?
3. Is there a dose response to the addition of vasopressin?

a. Study Design

15 hospitalized patients with refractory heart failure will enter a double-blind, placebo controlled study. After two days at a stable weight on maximal therapy, 5 patients in each group will be randomized to receive intravenously 1) placebo, 2) 0.3 mU/kg/min Vasopressin, 3) 0.6 mU/kg/min Vasopressin. Urine output and weight will be measured for the following 24 hours with no other change in medical regimen. If the systolic blood pressure increases to above 160 mmHg during the infusion, of study medicine-, -the rate of infusion will be decreased by one-half. After 24 hours, team physicians -may elect to continue the study medicine (particularly if it has been effective) as well as change the medical regimen. Data will continue to be recorded as long as the patient is hospitalized. Patients may continue the study drug until inotropic support is withdrawn or until discharge from the hospital.

b. Quantifying Outcome Variables

- 1) Urine output will be measured and recorded as per standard nursing protocol for the intensive care units.
- 2) Patient weights will be recorded daily. The same scale will be used for the same patient every day.

c. Statistical Analysis

15 patients will be randomized - 5 to each arm. This will give a power of 80% to detect a significant difference between each arm, assuming a 20% standard deviation within a person's daily urine output, and a 40% change from baseline urine output on the study medicine. Mean changes from baseline urine output will be calculated for each group. An unpaired T-test will be used to compare these means.

d. Method of Randomization

A randomization protocol will be used to determine treatment a patient will receive. Investigators and patient will remain blinded to treatment.

C. Description of Study Procedures

The duration of the study will be approximately 3 months. Appropriate patients will be referred by the CPMC CBF service. Daily rounds will be made in the intensive care units at CPMC to assess eligibility of patients not followed by the CBF team. These patients will be interviewed and examined by one of the investigators to determine eligibility. After randomization, eligible patients will continue to receive their medical regimen unchanged for the first 24 hours of infusion. Urine

output and weights will be collected as is standard among this type of patient. After 24 hours, patients may continue on the study medication until inotropic support is withdrawn, or the patient is discharged from the hospital, whichever comes first. After 24 hours, the medical regimen determined by the CHF team may be changed. Venous access will be required for the infusion of the study drug. Since all patients will require venous access for infusion of inotropic agents and a Swann- Ganz catheter in place for inclusion in the study, infusion of the study drug will not require additional placement of an IV line.

a. Protocol

1. Prior to initiation of the study each patient will be interviewed and examined by a study investigator to rule out exclusion criteria (see section G).
2. Once eligibility is determined, the research pharmacy will be notified for randomization to one of two vasopressin arms or the placebo arm." The research pharmacy will then send the appropriate study medicine to the patient's floor for IV infusion at a standard rate. Blinding will remain intact by using a double concentrated solution in the higher dose vasopressin arm, allowing all three arms use the same infusion rate. Prior to initiation of the infusion, a hemodynamic profile including cardiac output and cardiac index will be performed via the Swann- Ganz catheter. An investigator will be present for the first 30 minutes of drug infusion.
3. If a patient's systolic blood pressure increases above 160 mmHg, the infusion rate will be decreased by one-half. If this does not bring the systolic blood pressure below 160 mm. Hg, the patient will be removed from the study.
4. At 30 minutes, all patients will have their cardiac output and cardiac index measured again. If these values drop more than 25% the patient will be taken off the infusion. This is a necessary precaution given the severity of these patients illnesses.
5. All diuretics and inotropic agents will be maintained at pre-study doses for at least 24 hours after the initiation of study drug infusion. If the team following the patient determines that this is unsafe, the patient will be removed from the study protocol and adjustments made to the medical regimen. Such patient will be eligible for re-entry into the study once medically stabilized.
6. Treatment medication will be continued for 24 hours, but may be continued as long as inotropic support is needed.
7. Urine output will be charted every two hours (as per ICU protocol). SMA-7 will be sent two times every day to check the serum sodium. If the serum sodium is below 120 mEq/dL or drops more than 15 mEq/dL, the patient will be taken off the study medicine. Body weight will be charted each day of study medication.

D. Study Drug

Vasopressin will be infused intravenously at a rate of 0.3mU/kg/min or 0.6 mU/kg/min. It is currently approved at Columbia for use in vasodilatory shock at similar doses and for bleeding esophageal varices at >6 mU/kg/min. Only the low doses will be used in this protocol. Low dose vasopressin is well tolerated. At doses similar to those used in this study, patients on dialysis experience few to no effects (personal communication, D.W. Landry). At doses twice those used here, the most common side effects were reversible skin pallor and a sensation of warmth. At higher doses (>6mU/kg/hour), vasopressin is a potent vasoconstrictor. Complications at higher doses include upper and lower extremity ischemia, ischemic colitis, and myocardial infarction. There has been one report of death from Torsades de Pointes in a patient with prolonged QT syndrome during the infusion of vasopressin.

As addition of vasopressin may result in an experimental "Syndrome of Inappropriate ADIT", there is a risk of a drop in serum sodium. This has not been a problem in patients with vasodilatory shock from sepsis or endstage hemorrhagic shock (i.e. states of vasopressin depletion). It is unknown how frequently this complication will appear. In recent studies of vasopressin in severe heart failure, using doses similar to those planned in this study, there was no evidence of limb ischemia or myocardial infarction induced by vasopressin.^{11,13}

E. Medical Devices

No additional medical devices will be necessary.

F. Study Questionnaire

No questionnaire will be required.

G. Description of Study Subjects

a. Eligibility Criteria

- I. Hospitalized patients at New York Presbyterian older than 18 years, with congestive heart failure are eligible.
- II. Patients must be clinically volume overloaded (i.e. peripheral edema or rales on clinical exam) with a stable weight not varying more than 0.5 kg for two days, despite maximum strength diuretics. Maximum strength diuretic defined as at least two agents, one of which is a loop diuretic dosed equivalent to Lasix (furosemide) 400 mg per day.
- III. Patients must also be maintained on inotropic support with either milrinone or dobutamine in an intensive care unit.
- IV. Patients must have had daily weights and urine output for two days prior to randomization as per standard floor protocol.
- V. Patients must have a systolic blood pressure >85 mmHg and <160 mmHg, and a diastolic blood pressure >40 and <100.
- VI. Patient must have a Swann- Ganz catheter in place prior to enrollment.
- VII. Serum sodium must be > 120 mEq/dL.

b. Exclusion Criteria

- I. Patients with active angina or myocardial infarction at admission or during hospitalization will be excluded.
- II. Patients with a history of transient ischemic attacks, ischemic colitis, Raynaud's disease, or claudication will be excluded.
- III. Patients with a history of prolonged QT syndrome on EKG will be excluded.
- IV. As vasopressin will increase blood pressure, patients with pre-randomization blood pressures greater than 160 systolic or 100 diastolic will be excluded.
- V. Patients with end stage renal disease or renal failure requiring dialysis will be excluded. Patients with acute tubular necrosis will be excluded.
- VI. Patients with end stage liver disease will be excluded.
- VII. Patients with septic shock will be excluded.

H. Method of Recruitment

The CHF/cardiology service at New York Presbyterian Hospital will be review in-patient eligibility daily on rounds. An investigator will make daily rounds on ICU patients to determine eligibility of patients not followed by the CHF team. Identified patients will then be screened by an investigator, including a medical history and physical exam. Discussion with the patient, CHF team, and investigators will determine participation once eligibility is determined.

I. Confidentiality of Study Data

All patients will be assigned a number at randomization used for recoding and analysis of data. The assignments will remain at the Research pharmacy until the blind is broken for data analysis. Afterwards, all records will be maintained at the Principal Investigator's Office.

J. Potential Conflict of Interest

No conflict of interest exists.

K. Location of Study

The study will be conducted at New York Presbyterian Hospital.

L. Potential Risks

Patients will be at small additional risk of side effects from this dose of study medication. The most common anticipated side effects will be mild skin pallor and sense of warmth. Most patients are already at moderate risk for myocardial ischemia or ventricular arrhythmia, but there is little anticipated increased risk. As this hormone is found in excess in patients with Syndrome of Inappropriate ADH secretion, there is a risk of decreasing the patient's serum sodium during infusion. This is rapidly reversible upon cessation of the drug.

L. Potential Benefits

Potential benefits include 1) more rapid mobilization of retained fluid and lessened discomfort, 2) decreased time requiring inotropic support, 3) decreased length of stay in the hospital, 4) improved cerebral perfusion and sense of well being, 5) decreased need for dialysis or continuous venous-venous hemofiltration. The potential benefits to society include 1) improved treatment for a disease effecting hundreds of thousands of patients, 2) decreased hospital costs with shortened length of stay.

M. Alternative Therapies

There are few alternative therapies to this type of patient. One is cardiac transplantation which many patients are not able to obtain. Even if eligible, these patients frequently spend many weeks in the hospital awaiting transplant. The obvious advantage of heart transplantation is cure of the disease. The downside is its strict eligibility criteria and long waiting lists. Also, these patients require treatment during times they are awaiting a new heart. Another mechanism occasionally used is Continuous Venous Venous Hemofiltration/hemodialysis. This entails the insertion of a large bore catheter designed for dialysis into the femoral vein or internal jugular vein. The patient is then attached to a filtration machine that filters blood 24 hours a day, slowly removing fluid. It is much gentler on patient hemodynamics than standard hemodialysis. It has several downsides. It requires that the patient remain in bed 24 hours a day. It requires ICU monitoring/nursing care. It requires the insertion of a large bore catheter with its attendant risk of complications.

N. Compensation to Patients

There will be no compensation to patients.

O. Costs to Subjects

There will be no addition costs to subjects.

P. Minors as Research Subjects

Minors are not included in this study.

Q. Radiation and Radioactive Substances

No radioactive substances are involved in this study.

R. Gender and Minority Enrollment

It is anticipated that most of the enrolled patients will be part of minority populations. Differences in gender enrollment are not anticipated.

S. References

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