

# Protocol for very low dose Arginine Vasopressin for the Treatment of Hepatorenal Syndrome (PATH): A Double Blinded Randomized Controlled Trial

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## A. Study Description

### a. Study Purpose and Rationale

We have designed a protocol for the clinical investigation of a very low, non-pressor dose of arginine vasopressin (AVP) for the treatment of Hepatorenal Syndrome (HRS). HRS is a complication of end-stage cirrhosis characterized by progressive renal failure in the absence of an identifiable cause. HRS is common in patients with portal hypertension, with a prospective study in 1993 showing the 1 -year probability and 5-year probability in nonazotemic cirrhotic patients with ascites to be 18% and 39%, respectively.

HRS universally causes severe renal failure, and patients must be eventually maintained on dialysis, usually Continuous Renal Replacement Therapy (CRRT), for survival. The only definitive treatment is orthotopic liver transplantation (OLT), with a 3-year survival of at least 60%, only slightly lower than non-HRS transplant patients. A main goal of therapy for HRS, therefore, has been to "bridge" patients to OLT.

The etiology of HRS is related to the action of substances that cause dilation of visceral arteries, which leads to a complex neurohormonal response. This response eventually causes renal failure and death. Several therapies have been studied in humans, and have failed to improve renal hemodynamics and function. Others have shown some positive effects, but with prohibitive adverse clinical reactions. In several clinical trials in Europe, vasopressin analogs such as ornipressin and terlipressin appeared to reverse the renal dysfunction associated with HRS. The addition of intravenous albumin as adjunctive therapy likely improves the response. However, the trials have been small. Ornipressin is no longer in use due to toxicity, and terlipressin is not available in the United States. AVP, the only vasopressin available in the U.S., has not been studied prospectively.

This prospective, double blinded randomized controlled trial will test the efficacy of low dose vasopressin, compared to placebo, for the treatment of hepatorenal syndrome. Vasopressin (arginine vasopressin, AVP; antidiuretic hormone, ADH) is a peptide hormone released from the posterior pituitary gland. It is currently approved by the FDA for treatment of various conditions, including congestive heart failure, shock, and diabetes insipidus. Its primary function at normal physiologic levels in the body is to regulate extracellular fluid volume by affecting renal handling of water. In addition, at supra-physiologic levels, AVP has the following known effects in humans: 1) splanchnic vasoconstriction affecting liver-kidney neurohormonal interaction, 2) catecholamine suppression, thereby decreasing intrarenal vasoconstriction, and 3) in animals, AVP has been shown to reverse efferent arteriolar vasodilation in the glomerulus, thereby increasing the glomerular filtration rate (GFR). These three effects provide a clear physiologic rationale for the use of AVP for the treatment of hepatorenal syndrome in the setting of cirrhosis and portal hypertension.

## B. Study Design and Statistical Analysis

This prospective, double blinded randomized controlled trial will evaluate the efficacy of a very low dose AVP infusion with albumin for the treatment of hepatorenal syndrome.

Using the unpaired Mest, a total of 20 subjects with 10 subjects in each arm will be required to achieve 80% power and a Type I error of 0.05. However, we will recruit 20 subjects for each arm, as it is

difficult to predict the number of subjects who will require dialysis, receive transplants, or die prior to study completion. In addition, the larger "n" may also serve to increase the power of the study. Subjects will be identified by residents, fellows, and attendings in the emergency room, on hospital floors, and in the medical intensive care unit. However, subjects will only be recruited by the primary attending physician who must agree to enrollment in the study. Once the subject and his/her physician agree to participate, a study investigator will obtain informed consent from the subject. If the subject is unable to provide consent, the designated health care proxy may provide consent.

Eligible subjects will be those with hepatorenal syndrome, as defined by the International Ascites Club. Eligible patients will also have a foley catheter, which is standard of care for most patients with HRS. All procedures and patient encounters will be standard and necessary for the usual care of patients with HRS and end-stage liver disease. Liver transplantation will not be delayed or postponed to allow a subject to enroll in the study.

There will be two primary outcomes measured: 1) improvement in creatinine clearance by 30% 2) improvement in urine output to greater than 500 if baseline UOP is less than 300cc/day or doubling of daily UOP. Secondary endpoints will include decrease in serum creatinine and mortality. Because the predicted mortality of hepatorenal syndrome without orthotopic liver transplantation is greater than 90% within 2 weeks, mortality will not be a primary endpoint and will not be a factor in determining drug safety. Drug safety will be determined by daily monitoring for known vascular side effects of high dose AVP; the daily monitoring form incorporates a daily vascular exam to detect peripheral vascular compromise. In addition, lab tests, as described below, will be reviewed twice per day.

### C. Study Procedure

Informed consent will be obtained from the subject, and the investigator on call will be notified of subject enrollment. Subjects enrolled in the study will meet the International Ascites Club definition, which excludes other causes of renal failure and ensures adequate intravascular volume status. In addition, albumin level testing prior to beginning the administration of AVP will serve to ensure adequate oncotic pressure. If albumin is Less than 3g/dL, albumin will be repleted by either 25cc of 50% albumin or 250cc of 5% albumin; the choice between 25cc and 250cc will be based on the subject's volume status. Each subject's volume status will be determined by clinical judgment, using the subject's baseline blood pressure, orthostatics, and echocardiogram to assess intravascular volume. If a subject's volume status is unclear, PCWP may be determined either by RHC in the catheterization lab, or Swan Ganz catheterization in an ICU, or transduction of a central venous catheter in an ICU.

Subjects will be randomized to the vasopressin or placebo groups. Both the placebo and vasopressin formulations will be prepared and distributed by the research pharmacy. Subjects randomized to the vasopressin arm will receive fixed doses of weight-based AVP. Subjects who weigh 60-80 kg will receive 100 units of AVP in 100 cc NS @ 2 units/hr (0.033units/min= 0.033cc/min). Subjects who weigh less than 60kg will receive

100units in 100cc NS @ 1.5units/hr (0.025units/min= 0.025cc/min). Subjects who weigh more than 80 kg will receive 100 units in 100cc NS @ 2.5units/hr (0.041units/min= 0.041cc/min). Subjects randomized to the placebo arm will receive fixed doses of weight based normal saline. Subjects who weigh 60-80 kg will receive NS @ 2 units/hr (0.033units/min-- 0.033cc/min). Subjects who weigh less than 60kg will receive NS @ 1.5units/hr (0.025units/min-- 0.025cc/min). Subjects who weigh more than 80 kg will receive NS @ 2.5units/hr (0.041units/min= 0.041cc/min).

Subjects will remain on the continuous infusion of the placebo or vasopressin for at least 72 hours. Subjects will be classified as initial responders if creatinine clearance improves by greater than 30%, if UOP increases to greater than 500cc/day (assuming baseline UOP<300cc/day), or if UOP doubles from baseline. Initial responders respond will be maintained on the current "drug" until steady state is reached. "Steady state" is reached when the measured creatinine has not changed in 48-72 hours. If steady state is not reached within 72 hours, the subjects will be classified as initial responders but not sustained responders. Subjects who do not have a 30% increase in creatinine clearance and who do not have

improvement in UOP will be classified as nonresponders, and they will be released from the study protocol after the initial 72 hours. Subjects who die or require CRRT will also be classified as nonresponders. Both initial responders and sustained responders will be released from the study protocol at the end of "steady state." The primary teams will then decide to either continue the current "drug" or to make changes to the subject's medication regimen. The primary team, the investigators, and the analysts will remain blinded.

Stopping/changing the Protocol: Circumstances warranting changing the infusion of AVP include the following: 1) If a subject develops signs of ischemia: AVP will be decreased by one half or discontinued depending on severity, as determined by the principal investigator. 2) If there is an increase in a subject's systolic blood pressure to a) 30mmHg above baseline & >150mmHg OR b) >180mmHg, then AVP will be tapered by 0.5units/hour every eight hours until SBP <150mmHg. 3) If a subject develops signs or symptoms of allergic reaction to AVP, the infusion will be stopped immediately. If subjects develop an acute indication for dialysis and cannot be managed otherwise, AVP may be discontinued. Acute indications for dialysis include: hyperkalemia, acidosis, and volume overload refractory to medical management.

In both the vasopressin and placebo groups, subjects will have labs including chem7, ionized calcium, and albumin collected each morning and each afternoon. If albumin is <3g/dL, subjects will receive either 25% albumin 50cc IV every six hours or 5% albumin 250cc IV every six hours until the albumin is greater than 3gm/dL. Subjects will also have monitoring of their total daily urine output, and a daily creatinine clearance will be determined by a 3 hour urine collection during the time of the pm blood collection. The creatinine clearance will be calculated using the equation below.

$$\text{Cr Clearance} = (\text{Cr}) \times (\text{Vol}/2 \text{ hr}) / \{(\text{Cr}) \times (100\text{ml}/\text{dL}) / (120\text{ml}/2 \text{ hT})\}$$

\*Creatinine: measured in mg/dL. Volume: measured in dL

The following information will also be collected: subject gender, age, height, weight, race, ethnicity, child-pugh score, child-pugh grade, MELD score, date of admission, hospital LOS, disposition, presence of pre-existing renal insufficiency/comorbid diabetes/ hypertension/ascites, encephalopathy grade, type of hepatorenal syndrome, etiology of liver failure, and presence of precipitating event.

#### a. Endpoint

At the end of the study, daily urine outputs and creatinine clearances will be recalculated and compared for both groups of subjects.

Of note, all procedures and lab tests are considered to be part of the subjects' routine clinical management. The subjects will not undergo any procedures solely for research purposes.

### D. Study Drugs/Devices

Vasopressin (arginine vasopressin, AVP; antidiuretic hormone, ADH) is a peptide hormone released from the posterior pituitary gland. It is currently approved by the FDA for treatment of various conditions, e.g. congestive heart failure, shock, and diabetes insipidus. Its primary function at normal physiologic levels in the body is to regulate extracellular fluid volume by affecting renal handling of water. In addition, at supraphysiologic levels, AVP has the following known effects in humans: 1) splanchnic vasoconstriction affecting liver-kidney neurohormonal interaction, 2) catecholamine suppression, thereby decreasing intrarenal vasoconstriction, and 3) in animals, AVP has been shown to reverse efferent arteriolar vasodilation in the glomerulus, thereby increasing the glomerular filtration rate (GFR). These 3 effects provide a clear physiologic rationale for the use of AVP for the treatment of hepatorenal syndrome in the setting of cirrhosis and portal hypertension. Coronary artery disease is the only absolute contraindication to high dose AVP (>0.4units/min) therapy. High dose AVP has been associated with adverse effects on coronary blood flow, due to constriction of coronary arteries. Subjects with preexisting cardiovascular impairment may experience angina during the infusion of high dose AVP

because of these coronary effects. Studies using low dose AVP for the indication of septic shock only excluded subjects with known cardiovascular disease or subjects who were not adequately hydrated.

Albumin is a standard therapy used in patients with low serum albumin levels for maintenance of adequate intravascular volume. There are no significant contraindications to this medication. An albumin solution will be administered, as a fluid challenge in establishing the pre-protocol hemodynamic guidelines and as a means to maintain intravascular volume throughout the protocol. Different indications for AVP require different dosing regimens. Based on existing literature on the use of vasopressin analogues in HRS, we have chosen the following regimen: Subject's weight = 60-80 kg: 100 units of AVP in 100cc NS @ 2 units/hr (0.033units/min--0.033cc/min) Subject's weight < 60kg: 100units in 100cc NS @ 1.5units/hr (0.025units/min--0.025cc/min) Subject's weight > 80kg will receive 100units in 100cc NS @ 2.5units/hr (0.041units/min--0.041cc/min)

### **E. Medical Devices**

The study does not involve the use of medical devices.

### **F. Study Questionnaires**

The study does not involve the distribution or use of questionnaires.

### **G. Study subjects**

#### **a. Inclusion Criteria**

Subjects will be patients age 18 years and older who have chronic or acute decompensated liver disease with portal hypertension. They will meet the International Ascites Club definition for hepatorenal syndrome. Each subject will meet the following criteria:

- 1) Daily urine output less than 800 cc; foley catheter in place
- 2) Not intravascularly volume depleted or arterially underfilled (i.e. shock, sepsis), demonstrated by pulmonary capillary wedge pressure (PCWP) > or = to I 0mrnHg or central venous pressure (CVP) > or = 5mmHg and BP >90mmHg or BP that is not less than 30mmHg below baseline blood pressure
- 3) If Swan Ganz and central venous catheters are contraindicated, an echocardiogram. must show: no wall motion abnormality, absence of severe mitral and aortic valvular disease, and normal left ventricular filling.
- 4) Urine Na < I Omeq/L and FeNa < 1 % (off diuretic therapy)
- 5) Without another clear etiology of renal dysfunction (e.g. recent nephrotoxic medications or obstruction on USG)
- 6) Renal ultrasound with no evidence of vascular or outflow obstruction
- 7) Without sustained improvement in GFR after withdrawal of diuretics and fluid challenge of 1.31, (1 L saline times one + 50% albumin 50cc every four hours for 24 hours)
- 8) Peripheral capillary refill test < 2 seconds
- 9) Hernatocrit > or = 25%

#### **b. Exclusion criteria**

Subjects who have had a previous or current myocardial infarction, subjects who have known active coronary disease, and subjects who have congestive heart failure will be excluded from enrollment. Other exclusions include: active gastrointestinal bleeding; bacteremia; administration of diuretics, vasopressors, inotropes, fenoldopam, midodrine, or octreotide in the preceding 24 hours. Subjects are not excluded based on ethnicity, age, gender, or race.

### **H. Recruitment of subjects**

We will rely on the medical housestaff, gastroenterology and hepatology fellows, nephrology fellows, and attendings in the emergency department, medical intensive care unit, and on the general medical floors for subject identification. However, subjects will only be recruited for the study by the primary attending physician, who will determine if the subject is willing to discuss the study with a member of the study team. Flyers with the inclusion criteria will be posted in all of these locations. In addition, a noon conference on both HRS and the study will serve to educate the housestaff. At this conference, all housestaff will receive a pocketcard, outlining the selection criteria and study protocol. All nephrology, gastroenterology, and hepatology fellows will also be educated about the study; they will be instructed to contact one of the investigators, when they consult on patients who have hepatorenal syndrome. A contact person will be available at all times, via a pager, to answer questions regarding recruitment. In conjunction with informed consent, each subject's enrollment will be reviewed with his/her primary care physician.

### **I. Confidentiality of study data**

All labs and urine outputs will be recorded on a separate HRS data collection sheet, which will be placed in each patient's chart during the collection of data. This sheet will not become a part of the subject's permanent medical record. Data will be entered into a confidential electronic database on the Columbia Presbyterian Medical Center WebCIS system. Data files will be maintained in a secure computing environment, with access only for study personnel. Publications will not contain any personal identifiers of either subjects or their physicians.

### **J. Potential Conflict of Interest**

None of the investigators have a proprietary interest in the drug under investigation; none of the investigators will benefit financially from the results of the investigation.

### **K. Location of the Study**

This study will be conducted on the general medical floors of CPMC.

### **L. Potential risks**

Subjects may be randomized to placebo and may not receive the investigational drug; the condition of these subjects may continue to worsen. The protocol excludes subjects who are known to be at risk for adverse side effects of AVP. Risks that may exist despite the exclusion criteria include: failure to respond to AVP and progression of hepatorenal syndrome to death, severe allergic response to arginine vasopressin, peripheral vasoconstriction causing ischemic limbs (usually at higher doses), and central vasoconstriction causing ischemic bowel/other organs. In addition, subjects may have neck or groin catheter placement, which rarely causes bleeding, infection, and lung collapse.

### **M. Potential benefits**

We hypothesize that subjects with HRS, who generally have a >90% 3-month mortality, will receive a survival benefit from the action of AVP. Subjects who are candidates for OLT may survive long enough to undergo transplantation, the only known curative therapy of HRS. Additionally, patients receiving a therapy such as AVP through a detailed protocol are potentially more likely to be selected appropriately, and monitored more closely for both positive and adverse effects.

### **N. Alternative therapies**

There are no pharmacologic therapies that have been clearly shown to benefit subjects with HRS. Dialysis is a life-sustaining treatment that has no independent therapeutic value on the underlying disease. Orthotopic Liver Transplant is the only clear definitive therapy, which is difficult to access in a timely manner for the acutely ill subject. However, AVP off protocol, renal dose dopamine, midodrine and octreotide, prostaglandins, and diuretics are often used as alternative therapies despite their lack of proven benefit.

#### **O. Compensation to Subjects**

Subjects will not receive compensation for participation in this study.

#### **P. Costs**

Costs of all medical care will be billed to each subject or each subject's insurance company and will include all routine blood tests, all medications, and hospital stay. Of note, all procedures are routine for hepatorenal syndrome, and their costs will not differ from the costs that subjects would normally incur from hospitalization for hepatorenal syndrome. In addition, the cost of vasopressin is approximately fifteen dollars per day, and this represents a cost savings as compared to the cost of renal replacement therapy.

#### **Q. Minors as Research Subjects**

This study does not involve the participation of minors.

#### **R. Radiation or Radioactive Substances**

This study does not involve radiation or radioactive substances.