

Treatment Of Milrinone Induced Hypotension With Vasopressin

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A. Statement of study purpose and rationale

The standard of treatment of decompensated class IV congestive heart failure (CHF) usually involves positive ionotropic agents such as continuous infusion of dobutamine. When this is inadequate, or the patient is unable to tolerate the dobutamine, secondary to refractory tachycardia/malignant arrhythmia, phosphodiesterase inhibitors, such as Milrinone/Amrinone are commonly employed. The mechanism of action of these agents is believed to be secondary to the inhibition of Phosphodiesterase III (PDEIII) and to a lesser extent PDEIV.¹² The inhibition of PDEIII results in an intracellular accumulation of cyclic AW (cAMP) in both cardiac tissue and vascular smooth muscle. As a result patients usually exhibit both increased cardiac contractility, and peripheral vasodilatation resulting in increased cardiac output. Furthermore at higher dosages, Milrinone inhibits PDEIV, found in aortic endothelium, which results in the intracellular accumulation of cGMP and consequent further vasodilatation. Initial evidence in animals show that inhibition of PDEIV in the presence of increased cAW has a synergistic effect on decreasing vascular tone and possible hypotension.¹

Clinically, these agents may result in a marked increase in cardiac output and decrease in systemic and pulmonary vascular resistance (SVR, PVR)³. Studies in humans, testing intracoronary infusion of Milrinone have shown approximately 40% of Milrinone's increase in cardiac output is due solely to its positive ionotropic action, while the remaining 60% is due to its effect on vascular tone.⁴ Furthermore, some studies have shown a possible synergistic effect of combining Milrinone and traditional ionotropes such as dobutamine.⁵ Although initially promising, a small but significant percentage (between 3-10%) of patients are unable to tolerate Milrinone, especially at higher doses, because of profound vasodilatation⁶. When this occurs, further pressor agents must be instituted,⁷ or the Milrinone must be discontinued and other non pharmacological approaches such as balloon pumps, left ventricular assist devices and CVVH must be considered. Finally, even patients whose systemic blood pressure may be able to tolerate Milrinone, may still have a decrease in GFR secondary to efferent arteriole vasodilatation (relative intrarenal hypotension), thus possibly negating any positive renal effects gained via increasing cardiac output.⁸

Vasopressin is an endogenously occurring compound involved in the maintenance of vascular tone and free water resorption. In an ongoing trial, vasopressin is being investigated as a possible new agent in the treatment of vasodilatory/septic shock. These patients being characterized by high cardiac outputs and low SVR. Although the mechanism of action has not been fully elucidated, one possibility is that sepsis, besides resulting in a down regulation of vasopressin production (these patients are relatively vasopressin deficient), produces hypotension via Nitric Oxide intermediate. Nitric Oxide in turn, results in the intracellular accumulation of cGMP and subsequent vasodilatation.⁹ This is similar to the in-vitro effects of inhibition of PDEIV in aortic endothelium in rats. Vasopressin, via its VI receptor, has been shown to inhibit the intracellular rise of cGMP in rat aortic cells stimulated with ANF (Atrial Natriotic Factor)¹⁰, an endogenous vasodilator, which works by increasing levels of cGMP similar to Nitric Oxide. It has also been demonstrated that vasopressin will blunt the intracellular rise of cAMP in rat aortic smooth muscle stimulated by isoproterenol, resulting in contraction (or the inhibition of dilatation) of rat aortic smooth muscle.¹¹ In an ongoing trial, the use of low dose vasopressin in patients with vasodilatory shock has resulted in marked increased in blood pressure, reduction in the need for endogenous pressors, and increased urine output, without having a negative effect on cardiac output.

Recently, the open heart ICU (CTCU) has been using vasopressin on a large number of patients as a second line pressor agent. It has been difficult to ascertain the effectiveness of vasopressin in this

setting as the patients are frequently on numerous pressors with varying doses at the same time. The most striking observations to date has been that patients have tolerated the vasopressin remarkably well with increases in blood pressure at physiologic doses. The specific subgroup of patients who anecdotally appear to have the greatest benefit are those treated with the combination of Milrinone and vasopressin, where the latter was added for hemodynamic support. These patients have had dramatic increases in both urine output and blood pressure. One patient in particular was being treated for cardiac failure with dobutamine and dopamine. The patient was then started on Milrinone for continued poor cardiac output and anuria. The patient remained hypotensive and was started on vasopressin. Upon the institution of the Vasopressin, the patient's blood pressure increased from 90 to 130mmhg and urine output increased from 20-200cc/hr. The patient was eventually able to be tapered off all pressors and leave the intensive care unit. It is our hypothesis that Milrinone in some patients results in profound, uncontrolled, systemic vasodilatation and/or intra-renal vasodilatation, possibly due to the cross activation of PDEIV receptors and increasing endothelial cGMP. It is the profound vasodilatation could promote further hemodynamic instability or worsening renal dysfunction in the setting of an improved cardiac output. Vasopressin, which has proven effective in vasodilatory shock secondary to sepsis, possibly by modulating endothelial cGMP and maybe cAMP levels, may restore enough vascular tone to these patients to allow maintenance of adequate systemic and renal perfusion. Since we will be using doses of vasopressin 10-fold lower than traditional pressor doses (for GI bleeds), we believe it may show an advantage over traditional pressors; by not causing a pathologic increase in SVR and thus further decrease renal perfusion via excessive vasoconstriction. In addition, studies with Theophylline (also a phosphodiesterase inhibitor) have shown that it inhibits the release of vasopressin from rat neurohypophysis ¹² and therefore these patients may also be relatively vasopressin deficient.

The present study is designed to test the relative efficacy of vasopressin versus conventional pressors in patients with decompensated CHF. We believe that enough observational data currently exists from our CTCU and CCU to warrant a randomized double-blind placebo controlled trial. We have chosen only to include those patients on Milrinone since we believe that its vasodilating properties will allow these patients to have the greatest benefit but accrue the least risk from vasopressin. It is our hope that the addition of vasopressin will restore enough vascular tone to these patients such they will still be able to benefit from Milrinone's positive ionotrope effect, have some benefit from an overall reduced SVR, and be able to benefit from Milrinone's postulated synergistic effect with dobutamine in regards to increased contractility. The short term effect of this combination on patient hemodynamics, urine output and need for other pressor agents or non-pharmacological intervention will be evaluated.

B. Description of study design and statistical analysis

This will be a randomized, double-blind placebo controlled trial to take place at the CPMC CTCU, CCU, SICU or MICU. Initial eligibility (discussed in section G) will be determined by a diagnosis of CEF and inability to tolerate intravenous Milrinone.

All data will be analyzed to quantify the acute effects of vasopressin, relative to placebo, on Milrinone induced hypotension and the determination of serum vasopressin levels in these patients. Since initial data with patients in septic shock, and anecdotal data from the CTCU, show a dramatic decrease in pressor requirements (decrease of 1 Oug/min of Levophed) and increase in urine output, we believe that only 24 patients will initially need to be analyzed to show a statistical difference between vasopressin and placebo. All hemodynamic data, including blood pressure, SVR (when available), hourly urine output, and hourly use of conventional pressors will be compared between trial groups. Patient data size was calculated with the assumption of 1 Oug/min variance in baseline Levophed dose. If the variance is significantly greater, then covariant analysis, will be used to standardize according to baseline pressor requirements and hourly urine output. Baseline values will be obtained from data collection in the 1 hour prior to the institution of the study drug. Final endpoint data, average hourly requirement of Levophed for 24 hours, and average hourly urine output, will then be analyzed by Dr. Landry who will be blinded as to

which study medication the patient received. Vasopressin values will be compared to those already collected on patients with documented CBF (prior IRB) both on and off Milrinone.

C. Description of Study Procedures

All patients once deemed eligible (see section G), and informed consent obtained, will be randomized to receive either vasopressin or placebo. Patients will be assigned to either treatment group in advance via computer. All patients will then have a serum vasopressin level drawn while on Milrinone before the institution of vasopressin. Patients will then have their blood pressure recorded every 5 minutes for 20 minutes prior to the institution of the drug at which point the ICU nurse will be given a 250cc bag of D5W containing either vasopressin (100u/250cc D5W) or no medication. Only Dr. Hehn, Chen or Gold will know the content of the bag. The study medication will then begin infusion at 6cc/hr (0.04 units/min. of vasopressin). Blood pressure readings will be recorded every 5 minutes and urine output every hour. After 30 minutes, if the patient is normotensive and/or has at least a 50% decrease in Levophed requirement then the infusion will be maintained at 6cc/hr with BP measurements every 15 minutes and urine output every hour for 24 hours. After the initial 30 minutes, if the patient is still hypotensive and/or requires similar or increasing amounts of pressors (except Dobutamine), then the infusion rate will be increased to 12cc/hr (0.08units/minute Again, BP readings will be recorded every 5 minutes for 30 minutes. After this period the patient will be maintained at this rate for the next 23.5 hours (total study time 24 hours) with hourly urine outputs, and BP readings recorded every 15 minutes. After 24 hours the blinding will be removed and the ICU team in conjunction with the patient's physician can decide whether to continue or add vasopressin to the patient's regimen. Of note, if the patient has a Swan Ganz Catheter already in place, readings of cardiac output, pulmonary capillary wedge (PCW) and SVR will be obtained once before the institution of vasopressin, at each dosage of vasopressin attempted (minute 20 and 40 {if necessary}) and every 3 hours thereafter while the patient remains on vasopressin.

While on the study medication it will be the responsibility of the patient's study nurse to record the hemodynamic information as outlined above. Aside from the first hour of the trial, which has more frequent BP readings, the remaining readings are recorded at the same frequency as in standard ICU care and should not result in significant added work for the nursing staff. Furthermore, in order to standardize pressor requirements between the two groups, the nurses will be asked to adjust the patients pressor dosage to maintain a SBP between 90-100mmHg. The nurse will be asked to adjust the pressor every time she records a BP reading in the first hour and then at least once every 30 minutes thereafter (every other BP reading). This is also within the realm of standard nursing care.

The only restrictions on the ICU team will be that they can not adjust the Milrinone, for fear of increasing variability in the patient's pressor requirement. In addition, the ICU staff will be prohibited from starting any patient on open label vasopressin while enrolled in the trial. Finally The ICU team may discontinue the study medication at any time during the 24 hour period if the patient shows evidence of active myocardial ischemia (as defined in exclusion criteria section G) or new ventricular arrhythmia. Otherwise, the ICU team will be able to institute any other treatment modalities they believe necessary including diuretic agents.

All patients in the study will require a method for intravenous access (central line or peripheral intravenous catheter), an indwelling foley catheter, and an indwelling intraarterial line for continuous blood pressure readings. These are all standard tools of hemodynamic monitoring in an ICU and thus would be present in all patients regardless of their enrollment in this trial. Swan Ganz Catheters although preferred will not be required for this study.

D. Study Drugs

Vasopressin is an endogenous hormone with a short half-life of 10-20 minutes. Although usually given intranasally or intramuscularly for diabetes insipidus, it is also given intravenously at 0.9

units/minute as a vasopressor in the treatment of variceal bleeds. We plan to administer vasopressin at either 0.04units/minute or 0.08units/minutes, an order of magnitude less than the dose used for variceal bleeds, and equal to the doses used in septic shock. There are no described reports of anaphylaxis/hypersensitivity reactions. Majority of side effects will be hypertension.

Vasopressin will be prepared, by a member of the study team, as 100units/250cc D5W and infused intravenously at the above doses.

The side-effects reported with the use of intravenous vasopressin with variceal bleeds (again 10-15 times the dose used in this study) are similar to those of other conventional pressor agents. These include arrhythmia, cardiac arrest, gangrene, decreased urine output, increased SVR, hypertension and tremor. Of note that none of these have been observed with the use of low-dose vasopressin (0.04-0.08units/minute) in either the current trial with septic shock or anecdotally from the CTCU staff. Finally, we believe that use of low dose vasopressin will significantly reduce the requirement of these patients for conventional pressor agents which even at low doses have been observed to result in all of the above effects.

E. Medical Devices

None aside from those normally used in an intensive care unit.

F. Study Questionnaires

None

G. Description of Study Subjects and Method of Recruitment

Members of the study protocol will be notified of potential patients by the ICU staff and if deemed eligible the patient's physician will be approached by a member of the study protocol for permission for enrollment. If successfully obtained, then a member of the protocol, with or without the patient's physician, will personally discuss the protocol with the patient or her/his family if the patient is unable to give consent. A copy of the consent form is attached, and a Spanish version will be produced for those unable to speak and/or read English. At this time, the patient will be randomized to receive either vasopressin or placebo. The patient will be assigned according to a random assignment list generated by members of the study protocol before the enrollment of the first patient in the study. Only the members of the study protocol (excluding Dr. Landry who will analyze the data) will know which group the patient will be assigned to.

Eligible patients will have to have documented CHF (prior to the institution of Milrinone) (CI<2.5 liters/minute and SVR> 100 dynes by Swan Ganz Catheter or recent Right Heart Catheterization) or echocardiogram with left ventricular ejection fraction<25%, requiring intravenous ionotropic support (as determined by the ICU staff), who require but are unable to tolerate Milrinone for at least 1 hour. Inability to tolerate Milrinone will be defined as either symptomatic hypotension (dizziness, lightheadedness, oliguria, or need for intravenous pressor support) with a SBP<90, or asymptomatic patients with SBP<80. Patients will have to be on Milrinone for at least an hour to not only allow for the adequate collection of baseline hemodynamic data and pessor requirements, but also to eliminate those patients who have a small transitory drop in blood pressure with the initiation of Milrinone which usually resolves within 30-60 minutes.

Patients will be excluded if they are satisfactorily tolerating Milrinone, or if they have any evidence for systemic infection (36>Temperature>38, 4,000>WBC>12,000, positive blood cultures, new infiltrate on CXR consistent with infection). If patients exhibited any of the prior symptoms of infection within the previous 3 days, they must show documented improvement in any abnormalities (ie.- improved CXR, negative blood cultures, normal WBC/Temperature.. Patients will also be excluded if they show evidence of ongoing cardiac ischemia as determined by ST elevations in 2 consecutive leads> 1.5mm, or

new Left Bundle Branch Block. Patients will also be excluded if they have previously been treated with Vasopressin on this admission. No patients under 18 will be included in this study.

If a patient meets these requirements then she/he will be randomized as described in section C and the study will proceed as outlined above.

H. Confidentiality of Study Data

All data will be recorded in the patients ICU chart and kept strictly confidential. Any data removed from or copied off the patient's chart will be designated by a study number (to be chosen at random by the investigator) with the patient's actual name, unit number and corresponding study number kept on a list locked in one of the investigators desk. The manufacturer of intravenous vasopressin (Parke-Davis) may also have access to all patient data but again patients will be designated by a random study number. The patient's name and unit number will be kept strictly confidential.

I. Location of Study

Any patient at the CPMC CCU, MICU, Open Heart ICU, SICU or Allen Pavilion ICU will be eligible.

J. Risks/Benefits

The greatest risk to patients will come from increasing their SVR and thus possibly negating some or even all of the positive effects to be gained from Milrinone. However its use in the CTCU at these dosages have to date not demonstrated any of these problems. In addition, the patient can expect to have approximately 30cc of blood drawn during the study. Finally, the patient may accrue at most, 240 cc of additional fluid/24hrs. As the ICU team will be allowed to administer diuretics as they feel necessary, we feel that this small amount of fluid will be able to be successfully managed by the patient and the ICU staff and have no deleterious effect on the patient's hemodynamic and respiratory status over a 24 hour period.

Patients will benefit from this treatment as they may possibly avoid the need for other pressor agents to combat Milrinone induced hypotension. These agents (such as Levophed) unlike vasopressin can cause large increases in renal vascular tone and further decrease renal function (GFR). Furthermore, if able to tolerate Milrinone, patients may postpone or avoid the use of mechanical interventions for CHF such as intubation (for fluid overload), Intra-aortic Balloon Pump, Left Ventricular Assist device (if eligible) or Continuous Veno-Veno Hemofiltration (CVVH) (for intractable fluid overload).

K. Alternative therapies

The main alternative to the use of Vasopressin would be the use of a conventional pressor agent, or any of the non-pharmacological means described above. Patients will not be denied conventional pressors, if believed to be necessary (by the ICU) during the study.

L. Compensation

There will be no compensation for this study.

M. Minors

Minors will not be enrolled in this study.

N. Radioactive Substances

Not applicable to this protocol.

O. References

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TREATMENT OF MILRINONE INDUCED HYPOTENSION WITH VASOPRESSIN

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LAY SUMMARY**STUDY PURPOSE**

The purpose of this study is to determine whether patients who develop hypotension while being treated with Milrinone can be hemodynamically stabilized with low dose intravenous vasopressin. When patients with severe/decompensated congestive heart failure require intravenous pharmacotherapy they basically have two choices for ionotropic support. The first being dobutamine, a cardio-selective B-agonist which improves heart failure by increasing cardiac contractility. However, some patients can not tolerate this medication as it can cause lethal arrhythmias/tachycardias., while others, still are not hemodynamically stable even at the maximum dose of dobutamine.. Milrinone is a second line agent which improves heart failure by both increasing contractility and by dilating the patients vasculature. Thus increasing the "squeeze" and decreasing the resistance to that "squeeze". Although a very effective medication, some patients are unable to tolerate Nfilrinone secondary to hypotension as a result of its severe vasodilating properties. Thus patients who become/remain hypotensive on Milrinone must resort to either non-pharmacological interventions such as dialysis, or intra-aortic balloon pumps, or must be placed on other pressor agents such as epinephrine, or levophed. Currently, the CTCU (open heart ICU) has been treating such patients with numerous different pressor agents, including vasopressin. Vasopressin is naturally produced hormone which in recent trials with septic shock has proven to be effective in maintaining blood pressure at very low doses. As the hemodynamic profiles of patients with septic shock and Milrinone induced hypotension are similar, it is our hope that vasopressin will prove useful to these patients as well. If effective, then this combination of Wrinone and vasopressin may allow more patients with decomopnsated/severe congestive heart failure to remain free of conventional pressors or mechanical intervention.

Study Design and Procedure

This will be a randomized double-blind placebo controlled trial in which 10 patients with CHF who are hypotensive on Milrinone will be randomly assigned to receive either vasopressin or placebo (sugar water) for 24 hours. The primary endpoint for the study will be the patients average hourly requirement for other pressor agents as well as average hourly urine output. After 24 hours the trial will be over and the patient's primary physician will be allowed to dictate the patient's care.

The data will be analyzed which each patient being standardized according to their baseline requirement for pressor agents. Vasopressin levels will be compared to those with congestive heart failure on/off Milrinone which were obtained under a different IRB proposal. It is our hope that vasopressin will allow patients to either ".come-off" other conventional pressors and/or reach hemodynamic stability. As we expect a at least a 1 Oug/min decrease in Levophed requirements, we believe only 24 patients will be necessary.

All patients will be recruited from CPMC NIICU, SICU, CTCU, CCU. Permission will first be obtained from the patient's attending physician, and then informed consent will be obtained from the patient or patient's family if the patient is incompetent.

Although vasopressin, at high doses, has a similar side effect profile as conventional pressors, we believe that there will be no additional risk to these patients. Furthermore, as the dose of vasopressin used in this trial will be 10-fold lower than the conventional dose we expect a decrease in the occurrence of these adverse effects. Finally, we believe, that the data from the routine use of vasopressin on patients in the CTCU has adequately reinforced the above hypothesis on vasopressin's safety.