A Randomized, Placebo-Controlled Trial of Intravenous Administration of Low-Dose Dopamine in Hospitalized Patients with Acute Renal Failure

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A. Introduction

a. Rationale

Dopamine (DA), a precursor to epinephrine and norepinephrine binds to alpha, beta and dopamine receptors which are located in vascular smooth muscle cells of renal, mesenteric, coronary, cerebral, gastric and hepatic arterial beds. Stimulation of dopamine receptors promotes vasodilatation. Activation of DAI receptors in the proximal tubule inhibits Na-K-ATP and Na-H ion antiport activity, leading to natriuresis and diuresis. In addition, activation of DA2 receptors in the adrenal medulla and sympathetic nerve terminals reduces norepinephrine-mediated vasoconstriction. As these receptors are believed to be preferentially stimulated by intravenous infusion of small (renal) doses of dopamine, administration of renal dose dopamine (RDD) is a widely accepted practice in the setting of or to avert acute renal failure (ARF) and its use in the treatment of renal failure in adults is an FDA-labeled indication. Such benefit, however, has not been proven, and indeed a number of studies have provided conflicting results as to the renal benefit of low dose dopamine in the prevention of or recovery from acute renal failure.

Renal failure can be subdivided into three major categories:

(i) *Pre-renal:* this type of renal failure results from decreased renal perfusion, e.g. in the setting of hypovolemia or hypotension, decreased cardiac output, hence, decreased renal blood flow

(ii) *Intrinsic renal:* results from abnormalities within the kidney itself, e.g. at the level of renal blood vessels, glomeruli or tubules. Glomerular disorders may arise from diseases which generate immune complexes such as IgA nephropathy, post-strep glomerulonephritis, lupus, hepatitis, or AIDS-related. A number of drugs may induce interstitial nephritis (NSAIDs, antibiotics, diuretics, cimetidine or lead). A number of compounds are also toxic to renal tubules including pigments, contrast/dye, uric acid. Vascular disease may be secondary to mircroangiopathic disease (e.g. HUS, TTP), renal emboli, or again, may be drug-induced, e.g. intrarenal vasoconstriction in the setting of NSAID use.

(iii) *Post-renal:* refers to obstruction in the urinary system at any point past the renal calyces (usually kidney stones, BPH, malignancy, ureteral compression).

b. Literature Review

A number of studies have looked at the effects of renal-dose dopamine (RDD) on the prevention and reversal of renal dysfunction in a number of study groups. These have produced conflicting results largely secondary to non-uniform populations, small sample sizes, differing endpoints and varying methodologies:

In a randomized-control study of forty patients with normal heart and kidney function undergoing elective CABG, RDD offered no renal protection and may have exacerbated the severity of renal tubular injury during the early postoperative period (Tang et al, 1999).

A study including patients with established contrast-induced renal failure randomized 72 subjects to receive either saline or RDD.

48 hours after the procedure, the mean serum creatinine level was 2.4 mg/dI in the NS-treated group and 2.6 mg/dI in dopamine-treated group, the peak serum creatinine level was significantly higher in the dopamine than the saline group, and a greater percentage of patients treated with dopamine required

hemodialysis. Of note, there was a lack of information regarding fluid balance, body weight and the contribution of such to prerenal azotemia (Abizaid et al., 1999).

A study enrolling 55 patients with chronic renal undergoing aortography/arteriography received either renal-dose dopamine or saline. Dopamine infusion prevented a rise in serum creatinine 24 hours after angiography in patients with pre-existing renal insufficiency, and protected against contrast-induced decrease in renal function in patients whose baseline serum creatinine was > or = 2.0 mg/dI (Hans et al., 1998).

Renal dose doparnine was shown to have renal-protective effect in a study including 20 patients with severe CHF (Varriale and Mossavi, 1997).

Forty patients with diabetes mellitus undergoing coronary angiography were randomized to receive either RDD of dopamine prior to catheterization and continued for 6 hours afterward. RDD appeared to prevent deterioration in contrast-induced renal function as evaluated by serum creatinine levels between the two groups (Kapoor et al., 1996).

In a large cohort of septic oliguric patients (n=395), low-dose dopamine did not reduce the incidence of acute renal failure, the need for dialysis, or 28-day mortality (Marik and Iglesias, 1999).

Finally, a randomized-control study of 256 patients with ARF provided insufficient evidence that RDD improves survival or obviates the need for dialysis in persons with ARF (Chertow, et al., 1996).

B. Hypothesis

In patients with reversible acute renal failure, intravenous administration of renal-dose dopamine increases overall rate of renal recovery to baseline. In addition, due to an underlying complex interaction between renal function and a multitude of comorbid diseases, it is likely that administration of RDD may produce differential effects when results are stratified based on the underlying renal pathophysiology.

C. Methods

a. Conceptual and Operational Deflnitions

Outcomes to be measured include (1) determination of relative rates of recovery in the study and control groups patients who recover to their pre-study renal function; (2) determination of relative rates of recovery in the study and control groups patients who recover to a stable renal function, however, with subclinical defects in function; (3) determination of relative rates of progression to end-stage renal disease in study and control patients who will not recover function or who will progressively deteriorate; (4) determination of relative rates of death in both study and control groups.

Specific measured laboratory and physical parameters include daily BUN, serum creatinine, potassium, calcium, phosphate, weight adjusted urine output and volume status, until resolution of renal failure, until stabilization (ESRD or renal insufficiency) of renal function or until requirement of hemodialysis or death.

b. Study Design

The study will be a randomized, placebo-controlled, double-blind clinical trial. In-house patients who develop acute renal failure (defined by serum BUN>=25 and creatinine >=1.5), and those newly admitted who fall into the same category, will be selected. Exclusion criteria include patients with SBP < 100 and/or requiring pressors, patients with ESRD and/or requiring dialysis, and patients under the age of 18. Patients will be randomized to either (1) test group: continuous intravenous infusion of low-dose dopamine (2.5 mcg/kg/min) or (2) untreated control group: infusion of 0.9% saline at the equivalent rate. Both patients and primary medical doctors will be blinded to group assignment. All groups will be treated for 72 hours.

Each day, patients will undergo complete physical examination including assessment of heart rate, blood pressure, weight, volume status, above defined laboratory values, urine output and creatinine clearance. Serum potassium levels will be maintained at 4 mEq/L, fluid intake will be restricted to 1.5-2 L and patients will be prescribed a low sodium (2 g) diet. Intravenous DA will be suspended if monitoring

demonstrates increase in blood pressure or heart rate (20% over control), cardiac dysrhythmias or extravasataion of drug at IV site.

c. Statistical analysis

ARF complicates approximately 5% of hospital and 30% of ICU admissions and mortality is estimated at 50% (Brenner and Rector, 2000 Liberthal and Nigam). Of patients in the survival group, 40% will return to normal baseline renal function, 50% will have subclinical defects in renal function, 5% will have progressive deterioration of function, and 5% will have irreversible renal failure (Brenner and Rector, 2000).,

All data analysis will be performed on an intention to treat basis. Time of recovery to "baseline" renal function will be assessed using a Kaplan-Meier analysis in which %sick will be plotted vs. time. A chi-squared power analysis will be used to determine the number of patients required for enrollment.

d. Sample size

Determination of sample size will consider that the 50% mortality figure secondary to ARF will apply to both the treated and untreated groups, and that the overall effect of RDD is likely to present as a difference in time to recovery between the two groups. It is estimated that at an estimated intermediate point on the Kaplan-Meier curve, or '11/2", the proportion of renal recovery in the two groups will be approximately 20% in the placebo and 35% in the treatment-arm patients. Using the chi-square test, the sample size required for each group is 153.

In addition, results will be stratified further based on underlying etiology for renal failure: e.g. pre-renal vs. intrinsic renal vs. post-renal. Intrinsic renal will be further subdivided into glomerular vs. tubular vs. vascular dysfunction. In this way, it is hoped to further analyze differential physiological effects dopamine may produce on distinct renal functional components.

D. Study Drugs

Use of dopamine is an FDA Labeled Indication for renal failure in adults.

E. Medical Devices

N/A

F. Study Questionnaires

N/A

G. Study Subjects

Study participants must be at least 18 years old and have a serum BUN level >=25 and serum creatinine level >=1.5. Exclusion criteria include patients with SBP < 100 and/or requiring pressors, patients with ESRD and/or requiring dialysis.

H. Recruitment of Subjects

Subjects will be recruited from patients admitted to CPMC with new-onset ARF and to those patients in-house (on the floors and in the ICU, CCU, SICU) who develop ARF as defined above.

I. Confidentiality of Study Data

All study data will be confidential.

J. Potential Conflict of Interest

Neither the study investigators nor the hospital has a proprietary interest

K. Potential Risks

Dopamine is FDA-approved for the above-described indication. Harmful effects of this drug include tachycardia, increase in myocardial oxygen demand, dysrhythmias, respiratory depression and alteration in V/Q ratio.

L. Potential Benefits

As described above.

M. Refernces

Abizaid, AS, et al. Am. J. of Cardiology. 83(2):260-3, A5, 1999 Jan 15.
Brenner, BM and Rector, FC (eds.). The Kidney. 6h edition. Philadelphia, W.B. Saunders, Co.
Carcoana and Hines. Critical Care Clinics. 12(3) 677-685, July 1996.
Chertow, GM et al. Am. J. of Medicine. 101(l):49-53, 1996, Jul.
Cottee and Saul. Critical Care Clinics. 12(3) 687-695, July 1996.
Hans, BA, et al. American Surgeon. 64(5):432-6,1998 May.
Lieberthal, W and Nigam, SK. American Journal of Physiology. 278(i):FI-FI2, 2000 Jan.
Kapoor A., et al. International J. of Cardiology. 53(3):233-6, 1996 Mar.
Marik, PE and Iglesias, J. Am. J. of Medicine. 107(4):387-90, 1999 Oct.
Tang, AT, et al. European J. of Cardio-Thoracic Surgery. 15(5):717-21; discussion 721-2, 1999 May.
Varriale, P, and Mossavi, A. Clinical Cardiology. 20(7): 627-30, 1997 Jul.