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

A. Dopamine

- binds to alpha, beta and dopamine receptors located in vascular smooth muscle
- renal, mesenteric, coronary, cerebral, gastric and hepatic arterial beds
- Stimulation of dopamine receptors promotes vasodilatation
- Activation of DAI receptors in the proximal leads to natriuresis and diuresis
- activation of DA2 receptors in the adrenal medulla and sympathetic nerve terminals reduces norepinephrine-mediated vasoconstriction
- intravenous infusion of small (renal) doses of dopamine is believed to avert or ameliorate acute renal failure-- anFDA-labeled
- 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:* decreased renal perfusion
(ii) *Intrinsic renal:* within the kidney itself
(iii) *Post-renal:* obstruction in the urinary system at any point past the renal calyces

B. Literature Review

- It is generally agreed that renal dose dopamine augements RBF, GFR and natriuresis in several experimental models of ischemic and nephrotoxic ARF
- Most studies have failed to demonstrate a convincing prevention of ARF in high risk patients or an improvement in renal function or outcome in patients with established ARF
- ? Lack of true efficacy in humans
- ? Limitations in study design
- ? Lack of power
- ? Differential renal effects in "non-healthy" patients with co-morbidities
- e.g. renal vasconstriction by a revved-up rennin-angiotensin system may counteract any salutary effect of RDD

C. 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 co-morbid diseases, it is likely that administration of RDD may produce differential effects when results are stratified based on the underlying renal pathophysiology.

D. Outcomes

- determination of relative rates of recovery in the study and control groups patients who recover to their pre-study renal function
- who recover to a stable renal function, however, with subclinical defects in function
- who will not recover function or who will progressively deteriorate
- death
- measured laboratory and physical parameters include daily BT-N, serum creatinine, potassium, calcium, phosphate, weight adjusted urine output and volume status and will continue until resolution of renal failure, until stabilization (ESRD or renal insufficiency) of renal function or until requirement of hemodialysis or death.

E. Study Design

- randomized, placebo-controlled, double-blind clinical trial
- acute renal failure defined by serum BUN>=25 and creatinine >=1.5
- Exclusion criteria: SBP < 100 and/or requiring pressors, ESRD or under the age of 18
- Patients will be randomized to either
- test group: continuous intravenous infusion of lowdose doparnine (2.5 mcg/kg/min) or
- untreated control group: infusion of 0.9% saline at the equivalent rate
- Both patients and primary medical doctors will be blinded to group assignment
- groups will be treated for 72 hours
- daily complete physical examination
- volume status
- 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
- 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.

F. Statistical analysis

- ARF complicates approximately 5% of hospital and 30% of ICU admissions
- mortality approximately 50%
- for patients who survive:
- 40% will return to normal baseline renal function
- 50% will have subclinical defects in renal function
- 5% will have progressive deterioration of function
- 5% will have irreversible renal failure
- Time of recovery to "baseline" renal function will be assessed using a Kaplan-Meier analysis
- %sick will be plotted vs. time
- a chi-squared power analysis will be used to determine population size
- Determination will consider that the 50% mortality applies to both groups
- estimate that the effect of RDD is likely to present as a difference in recovery time between the two groups estimate that at an intermediate point on the Kaplan-Meier curve, or $t_{1/2}$, the proportion of renal recovery in the two groups will be approximately 20% in the placebo and 35% in the treatment-arms
- chi-square test sample size required for each group is 153

- results will be stratified further based on underlying etiology for renal failure:
- e.g: renal-dose doparnine may prove most beneficial in disease processes involving decreased perfusion (e.g. ischemic tubule cell injury) vs. those with etiology unrelated to renal blood flow (e.g. drug-induced interstitial nephritis)