The effect of Hydrochlorothiazide on Nighttime Blood Pressure Profiles in Non-Dipper Pre-Hypertensive Patients

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A. Study Purpose and Rationale

In patients with both normotension and essential hypertension, abnormalities in the circadian rhythm patterns of blood pressure profiles are predictors of larger cardiovascular outcomes. Individual blood pressure profiles typically vary in a diurnal pattern with blood pressure reaching its highest levels during daytime awake hours. Blood pressures subsequently fall to their lowest levels within the first few hours of sleep followed by a marked surge in the morning that corresponds with an individual's transition from sleep to wake. Patients that follow this classical pattern are referred to as "dippers," and they typically exhibit a reduction of 10-20% in their nocturnal systolic and diastolic blood pressures. In a significant number of normotensives and hypertensives, however, this nighttime blood pressure reduction is minimized and in a few patients, even increased. These individuals have been defined as "non-dippers," defined in a somewhat arbitrary manner as patients whose nocturnal systolic or diastolic BP dip by a value of less than 10%. Demographically, this pattern is exhibited at an equal level in males and females, and at higher levels within the elderly, type I and II diabetics, and most prominently in African Americans with a prevalence as high as 20-30%. Furthermore, this pattern increases in frequency with elevations in both systolic and diastolic blood pressure.

Recent literature suggests that these non-dipping patterns of blood pressure predict increased risk of cardiovascular disease and events independent of 24 hour ambulatory blood pressure profiles. Non-dipping patterns have been defined as an independent predictor of cardiac mortality (29) and stroke (42, 43, 63). They have also been associated with increased rates of ventricular and supraventricular arrhythmias (81), carotid disease (41), intracranial hemorrhages, and vascular dementia (44). At a pathophysiological level, non-dipping has been associated with increased left ventricular hypertrophy and QT prolongation.

The pathogenesis of non-dipping patterns are likely a result of multiple etiologies, including high levels of physical activity at night, highly active sympathetic systems, use of steroids, or the presence of underlying renal disease. In diabetics, autonomic neuropathy has been postulated as a predominant mechanism of non-dipping (24, 25). In the population of non-diabetic elderly and African Americans, recent data suggests that salt sensitivity and a failure of effective renal natresis is the major factor behind non-dipping in these respective populations. Minor improvements in non-dipping blood pressure patterns with salt restricted diets alone has been documented Therefore, diuretic therapy may offer a potent tool in effecting natresis and decreasing salt sensitivity in non-dippers with subsequent normalization of nocturnal BP.

We suggest that the use of a thiazide diuretic in non-dipping patients with pre-hypertension, as defined by JNC VII as BP 120-139/80-89 will result in a normalization of nocturnal blood pressure profiles. This could translate into significant long-term reductions in cardiovascular events and mortality using a cost-effective and simple to use medication with a fairly safe side

effect profile.

B. Study Design and Statistical Procedures

We are proposing a double blinded multi-center randomized controlled trial which will include two arms. Initially, patients will receive ambulatory blood pressure monitoring (ABPM) in order to select out patient with non-dipping patterns of nocturnal blood pressure. Selected subjects will receive education regarding lifestyle and diet control. They will then be randomized to either a thiazide diuretic dosed in the morning or to a matching placebo. Randomization will occur at the time of enrollment after receiving patients' informed consents. The general internist, patients, and investigators will be blinded regarding randomization. Data will be analyzed and followed by investigators.

The primary outcome will be the mean difference between the daytime and nighttime blood pressures – both SBP and DBP - measured at the time of randomization compared to 1 month after intervention. 1 month was chosen as the endpoint of this trial given the ability of thiazide diuretics to effect a physiological role well within this time period and also to allow for an upwards titration of thiazide dosing from 12.5 mg to 25 mg.

The number of patients necessary for this trial was determined by a power analysis with an unpaired t-test for continuous variables. This study was powered in order to detect a 15% difference between nocturnal blood pressure dips – calculated as the difference between daytime and nighttime blood pressures - between the intervention and placebo group. This value was based upon an assumption that thiazides can effect a similar improvement in nocturnal BP profiles as ACEI and calcium channel blockers studied in prior trials. From this analysis, we calculated that the study will therefore require 10 patients in both the intervention and control group in order to achieve a power of over 80%. However, our initial enrollment of patients will likely be 200-250 patients in order to ensure selection of non-dipper pre-hypertensives, and this enrollment will continue until a total of 20 non-dipper patients are obtained. This value is based upon preliminary data that suggests the incidence of non-dipper profiles to be as low as 7-10%.

Study Procedures

At the time of enrollment, recruited patients will first be trained to use validated oscillometric ambulatory blood pressure monitors by clinical nurses at the Behavioral Health and Hypertension Program, Columbia University Medical Center. These patients will then undergo 24 hour blood pressure monitoring with blood pressures taken at 20 minute intervals from 7 am to 11 pm and at 30 minute intervals from 11 am to 7 am. Technicians will pick up the monitors, from which subsequent data will be extracted at the Behavioral Health and Hypertension Program. There, nondipping nighttime blood pressure profiles will be selected out. These patients will then first receive lab data to assess for any underlying metabolic abnormalities, be randomized at the CUMC study center to either HCTZ or placebo by research coordinators. Patients will again receive 24 hour ambulatory blood pressure monitoring at 1 week into the study to allow for up-titration of HCTZ dosage and finally at the 1 month mark in order to assess the effect of HCTZ on nocturnal BP profiles. At one week following initial randomization, patients will receive a basic metabolic panel blood test in order to determine any metabolic effects of HCTZ.

D. Study Drugs or Devices:

Hydrochlorothiazide (HCTZ): HCTZ is a part of the thiazide diuretic class of medications. Its mechanism of action is to inhibit absorption of sodium mainly at the distal convoluted tubule by inhibition of the thiazide sensitive sodium/chloride cotransporter. It is an approved indication for the treatment of HTN. Its dosing ranges from 12.5 mg to 50 mg PO qd, however, it has primarily Contraindications to its use include anuria and hypersensitivity to sulfonamides. Side effects of HCTZ include weakness, muscle cramps, impotence, hypokalemia, hypomagnesemia, hyperlipidemia, hypercalcemia, hyperglycemia, hyperuricemia, and hypnatremia. Limiting HCTZ to low doses (12.5-25.0 mg) can minimize these side effects. The dosage of HCTZ works on blood pressure via mainly its diuretic effect; vascular effects are seen at primarily higher doses.

Medical Device: The oscillometric ambulatory blood pressure device we will use is the **A&D TM-2421** which has been validated by protocols of the British Hypertension Society. This device contains multiple size cuffs, weighs 370 grams with dimensions of 150 x 80 x 45, and comes with a rechargeable battery unit. The cost of the device is $2162.00 including all relevant software.

E. Study Questionnaires

Enrolled subjects will complete study questionnaires regarding their exercise and diet habits at the initiation of the study, at weekly intervals throughout the study, and at the close of the study. The importance of these records is reflected by the effect that both exercise and diet have upon nocturnal blood pressure profiles. In effect, differences between the study groups can be controlled for by the use of this data.

F. Study Subjects:

Patients will be enrolled who have documented pre-hypertension, as defined by recorded mercury sphygomometer measured blood pressures at two or more clinic visits that range between 120-139/80-89. Patients will be enrolled from ages 25 to 65 and will be inclusive of all genders, ethnicities, and races.

Exclusion Criteria:

1. JNC VII defined hypertension
2. renal disease (Cr>1.5 mg/dl)
3. diabetes mellitus
4. coronary artery disease and/or heart failure
5. pregnancy
6. COPD

7. Absolute or relative contraindications to thiazide

G. Recruitment:

Patients will be recruited from the Division of General Medicine clinics and affiliated private practices of the following medical centers: Columbia University Medical Center, Harlem Hospital Center, and St. Luke's-Roosevelt Hospital. These three medical centers will reflect a diversity of New York City patient populations. Internists in these respective divisions will be approached by study coordinators either in person or by phone. Involved physicians will then have the responsibility to select appropriate pre-hypertensive patients for this study, following which they will refer them to the study center at Columbia University Medical Center.

H. Confidentiality of Study Data:

Each patient will receive a coded identification number and all data will be stored securely at the study center at the Behavioral Health and Hypertension Program on PH-9.

I. Potential Risks:

The potential risks of this study are minimal and are primarily based upon possible side effects of HCTZ. Patients will also receive basic metabolic panels at 1 week following the initiation of the medication in order to ensure minimal metabolic side effects of the medication,

J. Location of Study:

The study will be carried at out at the Behavioral Health and Hypertension Program Center, Columbia University Medical Center at PH-9; as well as in individual homes regarding 24 hour blood pressure monitoring.

K. Potential Benefits:

A potential benefit of this trial is that subjects will be able to receive an accurate impression of their blood pressure profiles from ambulatory blood pressure monitoring, which is considered to be more accurate than office blood pressures. In fact, while not covered by Medicaid and Medicare, pre-hypertension is seen as an indication for ambulatory blood pressure monitoring. Also, at a larger level, the use of thiazide diuretics may prove to be a cost effective measure of normalizing non-dipping status in normotensive and hypertensive patients, allowing for subsequent improvements in long-term cardiovascular outcomes.

L. Alternatives (to participating in the study for the pt):

N/A

M. Compensation:

Patients will not be financially compensated for their participation in this trial.

N. Costs to Subjects:

No costs will be incurred at the expense of participating patients. Costs of medications and device use will be covered by the study investigators.

O. Minors as Research Subjects:

N/A

P. Radiation or Radioactive Substances:

No radiation nor radioactive studies will be part of this study.

Q. References: