The effect of different classes of antihypertensive medications on ambulatory blood pressure

Shepard Weiner

A. Study Purpose And Rationale

According to the National Health and Nutrition Examination Survey (NHANES), conducted by the National Center for Health Statistics, from 1999-2000, almost 29% of the adult U.S. population had hypertension. Of these individuals, 69% did not have their hypertension controlled (JAMA 2003; 290(2):199-206).

Ambulatory blood pressure monitoring is a non-invasive, fully automated technique that records blood pressure over an extended period of time, usually 24 hours. During a typical monitoring session, blood pressure is measured every 30-60 minutes, including both awake and sleep hours. It is important to recognize ambulatory blood pressure monitoring as a valuable tool in the clinician's assessment of hypertension. Specifically, it can be used to a determine a patient's blood pressure outside the office and therefore identify individuals with white-coat hypertension, masked hypertension, or a non-dipping nocturnal blood pressure pattern (Pickering AHA Scientific Statement on Hypertension 2004).

Recent evidence suggests that 24 hour ambulatory blood pressure readings predict risk of cardiovascular events better than office blood pressure (NEJM 2003; 348(24):2407-2415; JAMA 1999;282:539-546). Furthermore, it has been demonstrated that the effect of antihypertensive therapy is greater on office blood pressure than ambulatory blood pressure (Journal of Hypertension 2004; 22(3):435-445). Therefore, this study will examine which class of antihypertensive medical therapy is most effective in lowering ambulatory blood pressure.

Hyperactivity of the sympathetic nervous system, assessed directly in the clinical setting, has been implicated in the pathogenesis of essential hypertension and in the development of target organ damage (Am J Hypertens 1996;9:113s-120s). Using the technique of microneurography to quantify sympathetic discharge, an increase in the mean frequency of bursts has been reported in patients with essential hypertension compared with matched normotensive controls (J Hypertens 1999; 17:719-34). Therefore, if Bblockers directly diminish this hyperactivity, they may prove to be more effective in decreasing ambulatory blood pressure and cardiovascular outcomes due to hypertension.

Hypothesis: Bblockers are more effective in reducing mean 24 hour ambulatory blood pressure than thiazide type diuretics, dihydropyridine calcium channel blockers, or angiotensin converting enzyme inhibitors since they attenuate the control mechanisms that contribute to the dynamic nature of blood pressure.

The results of this study will have significant implications. The Seventh Report of the Joint National Committee on the classification of and treatment recommendations for prehypertension and the stages of hypertension are based primarily on data from studies that measured office blood pressure. However, a reduction of blood pressure below hypertension thresholds based on office blood pressure does not automatically translate to a similar effect on ambulatory blood pressure. This makes it necessary to determine which medication classes most effectively reduce ambulatory blood pressure.

B. Study Design And Statistical Analysis

The study will include four groups. The subjects will be randomly assigned to either receive metoprolol, chlorthalidone, amlodipine, or lisonopril. All eligible subjects will be enrolled at the time their individual physicians were scheduled to initiate pharmacotherapy since therapeutic lifestyle changes were insufficient for blood pressure control. Treatment with the study drug will be initiated the day after randomization. The subjects will be randomly assigned their study drug by telephone.

The primary endpoint will be the number of subjects in each study group with a mean 24 hour ambulatory blood pressure <130/80 at four months. Secondary outcomes will include the number of subjects in each study group with a mean daytime (8AM-8PM) blood pressure <135/85 at 4 months and the number of subjects in each study group with a nighttime (8PM-8AM) blood pressure <120/70 at 4 months. Additional secondary outcomes will include the mean ambulatory blood pressure from the hours of 6AM to 11AM in each study group to represent the AM surge as well as the mean ambulatory blood pressure from the hours of 12AM to 5AM in each study group to represent the nocturnal dip in blood pressure. Normal ambulatory blood pressure values have been established in two ways. First, by comparison of the ambulatory blood pressure level that corresponds to a clinic pressure of 140/90 and, second, by relating ambulatory blood pressure to risk in prospective studies. Four months was selected as the time of the endpoint since it allows for sufficient time to reach uptitration of each study group in order for control of ambulatory blood pressure to occur with monotherapy. At this point, if a maximally dosed study drug cannot control a subject's ambulatory blood pressure, it is unlikely to do so, even with further time.

The number of subjects needed was determined by a power analysis with a chi-sqaure test to compare proportions of a categorical outcome, namely, the number of subjects in each group with a mean 24 hour ambulatory blood pressure <130/80 at four months. Three hundred and eighty two subjects will be required in each group for the study to achieve a power of 80 percent to detect a 10 percent difference between the Bblocker and other study groups in the rate of ambulatory blood pressure control. This power analysis is based on achieving a 70% success rate in the metoprolol group and a 60% success rate in the chlorthalidone, amlodipine, and lisinopril groups. These numbers assume the smallest difference of clinical significance to be 10%. Approximately 50% of all hypertensives can be successfully controlled on monotherapy. Since this study is going to enroll subjects with only Stage 1 essential hypertension, the success rate is expected to be higher than the average value of 50%.

The randomization will occur in a double blinded fashion. The study drugs will be encapsulated and identical in appearance.

The subjects that fail to become normotensive based on ambulatory blood pressure after uptitration of the study drug will have an additional drug, selected from one of the other groups, added in an open-label fashion at the individual physician's discretion. At this point, these subjects will have been classified as not successfully meeting the primary endpoint. In order to ensure proper management of their hypertension, their physicians' will be made aware of those subjects' study drug, independent of the investigators of the study. These patients will have the option of continuing to use the ambulatory blood pressure monitoring device for the four month study period.

The statistical analysis will also use the chi-sqaure test to compare the proportion of subjects who were successfully managed on monotherapy in each study group. Additionally, statisticians may need to do multiple logistic regression to account for other factors that may contribute to ambulatory blood pressure control, such as diet and exercise.

C. Study Procedure

At enrollment, blood pressure will be measured by trained study nurses using a mercury sphygmomanometer in all eligible subjects. The ambulatory blood pressure cuff will be placed on the non-dominant arm, and a series of calibration readings taken with the mercury sphygmomanometer will be performed to ensure that the device is giving accurate readings within 5mmHg of the mercury readings. Immediately after the visit, ambulatory blood pressure will be recorded over a 24-hour period during the patient's normal daily activities, with the use of properly validated and calibrated monitors programmed to obtain readings at intervals of not more than 30 minutes between 8 a.m. and 8 p.m. and at intervals of not more than 60 minutes between 8 p.m. and 8 a.m. Raw data will be sent to the coordinating center and visually inspected by a technician before being entered into the central data base. A subject who cannot transmit the information from home will be required to come to the study center. No specific editing criteria will be applied to the blood pressure readings. The ambulatory blood pressure monitoring

will be performed weekly and uptitration of study drug medication will be done at two week intervals if the goal ambulatory blood pressure is not being met. Additional medication will be added at the visit following the visit where the study drug was maximally titrated if the mean 24 hour ambulatory blood pressure remains >130/80. This procedure will be carried out both for research purposes and for the clinical management of subjects. Ambulatory blood pressure monitoring has been used for many years as a research procedure, and is now approved by Medicare for reimbursement in patients with suspected white coat hypertension.

The standard equipment includes a blood pressure cuff, a small monitor that can be attached to a belt, and a tube connecting the monitor to the cuff. A trained study technician will place the device on the patient, provide instructions to the patient, and then download data from the device when the patient returns if unable to do it outside the study center. The Suntech Medical device is validated by the American Association of Medical Instrumentation (AAMI). Although the subjects may initially experience some discomfort, the device is non-invasive.

The anticipated duration of the study is four months. Each subject's participation is expected to last until they fail the study drug or four months. A certain number of subjects may end up participating for a shorter period of time secondary to study drug or device nonadherence. All subjects will be included in the statistical analysis satisfying the principle of intention to treat.

D. Study Drugs

Four commonly prescribed antihypertensive medications will be used in this study.

1. Metoprolol will be the study drug from the Bblocker class. Treatment of hypertension is an approved indication. Initial doses are 50-100 mg orally once daily. For titration, allow 1-2 weeks to achieve optimum antihypertensive effect. Usual maintenance doses are 100-400 mg orally once daily. Contraindications include cardiogenic shock, hypersensitivity to metoprolol, overt cardiac failure, second and third degree AV block, severe sinus bradycardia, and sick sinus syndrome. Precautions include anesthesia/surgery (myocardial depression), avoid abrupt withdrawal, bronchospastic disease, congestive heart failure, diabetes mellitus, hyperthyroidism/thyrotoxicosis, liver disease, and peripheral vascular disease. Common adverse effects include bradycardia (3%), cold extremities (1%), heart failure (1%), hypotension (1%), depression (5%), dizziness (10%), headache (10%), tiredness (10%), constipation (1%), diarrhea (5%), dyspepsia (1%), nausea (1%), dyspnea (3%), wheezing (1%), pruritus (5%), and rash (5%). Serious adverse effects include bronchospasm (1%).
2. Amlodipine will be the study drug from the dihydropyridine calcium channel blocker class. Treatment of hypertension is an improved indication. Initial dose is 5 mg orally once daily. Maintenance dose 5-10 mg orally once daily. Contraindications include hypersensitivity to amlodipine. Precautions include aortic stenosis, CHF, exacerbation of angina during initiation of therapy or after dose increases or withdrawal of beta blocker therapy, hypotension (initially or after dose increases),liver impairment, and persistent progressive dermatologic reactions. Common adverse effects include dizziness, fatigue, flushing, headache, palpitation, and peripheral edema. Serious adverse effects include myocardial infarction, angina, and arrhythmia (rare).
3. Chlorthalidone will be the study drug from the thiazide type diuretic class. Treatment of hypertension is an approved indication. Initial dose recommended is 12.5 mg orally once daily. For titration, increase dose to 25mg once daily and then to 50 mg as single daily dose if necessary. Maintenance doses are often lower than initial doses and should be adjusted according to the individual patient. Contraindications include anuria and hypersensitivity to chlorthalidone or other sulfonamides. Precautions include avoiding lithium, diabetes mellitus, electrolyte imbalance, history of allergy or bronchial asthma, hyperuricemia or gout, hypotension, impaired hepatic function or progressive liver disease, may aggravate digitalis

toxicity, severe renal disease, and systemic lupus erythematosus. Common adverse effects include hypotension, vasculitis, dizziness, headache, paresthesias, restlessness, anorexia, constipation, diarrhea, nausea, vomiting, electrolyte abnormalities, hyperglycemia, hyperuricemia, blurred vision, xanthopsia, impotence, photosensitivity, phototoxicity, and muscle spasms. Serious adverse effects include arrhythmias (rare), blood dyscrasias (rare), exfoliative dermatitis (rare), hepatotoxicity (rare), pancreatitis (rare), pulmonary edema (rare), Stevens-Johnson syndrome (rare), systemic lupus erythematosus (rare), and toxic epidermal necrolysis (rare).

4. Lisinopril will be the study drug from the ACE inhibitor class. Treatment of hypertension is an approved indication. Initial dose is 10mg orally once daily. Usual maintenance doses are 20-40mg orally daily, with maximum dose of 80mg per day. Lisinopril will be dosed two times per day in this study. Contraindications include ACE inhibitor-induced angioedema, history of angioedema, hereditary or idiopathic angioedema, hypersensitivity to lisinopril or other ACE inhibitors, and pregnancy. Common adverse events include cough, dizziness, headache, hyperkalemia, hypotension, nausea/vomiting, and rash. Serious adverse events include
angioedema - face, lips, or throat (rare; more frequent in Black patients), intestinal angioedema, and renal dysfunction (2% of AMI patients)

E. Medical Device

This study is not testing a medical device but it does employ the use of an ambulatory blood pressure monitor. The Suntech Medical Oscar 2 is an ambulatory blood pressure monitoring device that is commercially available. Its features include oscillometric technology, quick hook-up, cuff size recognition, quiet operation and compact proportions that aid patient compliance, and low power consumption requiring only two AA batteries. The accuracy is reported as ±3mmHg compared to mercury sphygmomanometry. The dimensions are 12cm x 8cm x 3cm and the weight is 284 grams including batteries. There is a liquid crystal display and PC interface through a serial interface with 9 pin RS232 connector. The recording duration is up to 52 hours and options include multiple cuff sizes. The sample quantity includes over 250 samples of systolic pressure, diastolic pressure, computed MAP, and heart rate.

F. Study Questionnaires

This study will have two questionnaires, a food frequency and exercise frequency questionnaire that will be completed at the time of enrollment and at conclusion of the four month study period. Diet and exercise influence blood pressure. By collecting this data, it can be used in statistical analyses to control for any differences between the study groups. This will allow for determination of the effect of study drug while also being able to report on any differences in diet or exercise.

G. Study Subjects

The prerequisite for inclusion will be documented hypertension at two separate office visits within a one year period before enrollment. Hypertension will be diagnosed if the mean of two sphygmomanometric readings (obtained in the office, when the subject is sitting, after five minutes of rest) of systolic blood pressure exceeds 140mmHg or diastolic blood pressure exceeds 90mmHg. At the time of enrollment all subjects will have already attempted therapeutic lifestyle changes as recommended by their physician. Physicians will be given guidelines for what constitutes failed therapeutic lifestyle changes as stated by the NCEP ATP III. In order to be eligible, the subjects will have to be willing to give informed consent. Subjects of either gender, of all racial and ethnic groups, English as well as non-English speaking populations, between the ages of 55 and 84 will be eligible. Pregnant women and

women contemplating pregnancy will be excluded given the possibility of randomization to an ACE inhibitor. Criteria for exclusion include history of Stage 2 Hypertension according to JNC 7 classification (>160mmHg SBP or >100mmHg DBP), suspicion of secondary hypertension, diabetes mellitus, personal history of coronary artery disease or heart failure, serum creatinine concentration more than 2.5mg per deciliter, chronic obstructive pulmonary disease, and refusal to undergo repeated follow-up visits and ambulatory blood pressure monitoring.

H. Recruitment Of Subjects

Academic Departments of Medicine and Divisions of General Internal Medicine in the New York metropolitan area will be approached to participate in the project. Internists will be approached by letter of invitation and contacted by a medical coordinator either at a face-to-face meeting or by telephone. Additionally, peer-to-peer recruitment will be adopted. Therefore, recruitment of subjects will be through each subject's primary physician and that physician will need to agree that the subject is suitable for study and ascertain from the subject that he/she is willing to discuss the study with the research team before any approach may be attempted by the investigators.

I. Confidentiality Of Study Data

The study data and identity of study subjects will remain confidential. The data will be coded. A unique code number will be generated for all subjects. A personal identifier will not be used. The data will be stored at the Behavioral Cardiovascular Health and Hypertension Program, Columbia University Medical Center, and will only be accessible to the investigators.

J. Potential Conflict Of Interest

The investigators or the University do not have a proprietary interest in the drugs being tested or the device being used and do not stand to benefit financially from the results of the investigation.

K. Location Of The Study

This study will be based out of New York-Presbyterian Hospital, Columbia University Medical Center. The Department of Medicine and its affiliated clinics, as well as practices and clinics in the metro area, will serve as study sites.

L. Potential Risks

The medical risk to subjects in this study is minimal to none. All subjects will be receiving antihypertensive medical therapy that is FDA approved to control blood pressure. There is no placebo arm of the study. It has been shown that 24 hour mean blood pressure is not reduced by placebo and it is not necessary to include a placebo control group in antihypertensive drug studies in which ambulatory blood pressure monitoring is employed (Am J Hypertens 1995 Mar; 8(3):311-315).

Subjects of all ethnicity and race will be eligible. Although not standard of care, it has been observed that certain races have traditionally had better experience with specific classes of antihypertensive medications. It is possible that a subject will be randomly assigned a study drug that may not conform to these perceptions. However, each subject will have his/her blood pressure accurately and aggressively monitored, and will have an addition or substitution of antihypertensive medication made if he/she fails monotherapy with the study drug in a timely fashion.

The subjects may experience minimal discomfort from the ambulatory blood pressure monitoring device.

At the two month visit, all subjects with have a laboratory test performed to assess a basic metabolic panel to ensure that no electrolyte disturbances resulted from the study treatment. The results will be reviewed by the Data and Safety Monitoring board.

M. Potential Benefits

The subjects in the study may benefit from their involvement since the device being used to monitor their blood pressure is a better predictor of cardiovascular outcomes than office BP readings. The subjects may not benefit if their ambulatory blood pressure cannot be adequately controlled on the study drug and the protocol for uptitration and adding open label agents. Therefore, the subject may or may not benefit as a result of participating in this study. This study has potential benefit for society. If a cost-effective treatment for ambulatory blood pressure can be established this will benefit the hypertensive members of society that this study applies to.

N. Alternative Therapies

The study does not involve experimental therapies. All the drug therapies are approved. Based on the exclusion criteria, no subject will have a specific class indication for an alternative antihypertensive agent.

O. Compensation To Subjects

The subjects will not be financially compensated for their participation in the study.

P. Costs To Subjects

The subjects will not incur any additional costs as a result of participating in the study. The ambulatory blood pressure monitor and expense of any health care provider visits, including transportation to and from that encounter, will be paid for by the study. The subjects' study drugs will be paid for, either through the subjects' prescription drug plan or by the study sponser.

Q. Minors As Research Subjects

The study does not involve the participation of minors.

R. Radiation Or Radioactive Substances

The study does not involve any radiation or radioactive substances.