Treatment of Orthostatic Hypotension

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Protocol and Statistical Analysis Plan

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Project Title: **The Treatment of Orthostatic Hypotension**
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Principal Investigator: David Robertson, M.D., Professor of Medicine, Pharmacology and Neurology

Co-Investigator(s): Emily Garland, Ph.D., Division of Clinical Pharmacology
Paula Yamhure, RN, Division of Cardiology
Italo Biaggioni, MD, Departments of Medicine and Pharmacology
Satish Raj, MD, Division of Clinical Pharmacology
Bonnie Black, RN, Division of Cardiology
Indu Taneja, MD, Division of Clinical Pharmacology

HYPOTHESIS

We propose that a systematic trial of medications in patients presenting with a unique and chronic constellation of symptoms of autonomic dysfunction will provide us with information on the pathophysiology of their condition and assist us in optimizing their treatment.

SPECIFIC AIMS

To give a single dose of one or more drugs to determine the effect on orthostatic hypotension in a group of patients with autonomic dysfunction of unknown pathophysiology. Depending on the results of these single-dose trials, we might subsequently do 5-day trials and chronic (approximately 2 months) trials.

BACKGROUND AND SIGNIFICANCE

Norepinephrine (NE) and epinephrine (E) are critical determinants of blood pressure. Moreover, they are also involved in the regulation of autonomic outflow in the brainstem and spinal cord. In the periphery, NE is pressor, but within the central nervous system (CNS) it often depresses sympathetic outflow, resulting in a fall in blood pressure. Thus, any factor that alters the synthesis of these catecholamines can perturb blood pressure at several interacting levels. Tyrosine hydroxylase [(tyrosine to L-dihydroxyphenylalanine (DOPA)] is the rate-limiting step in NE synthesis under almost all circumstances. DOPA decarboxylase converts DOPA to dopamine (DA). Dopamine-ß-hydroxylase (DBH) converts DA to NE. Loss of DBH leads to an inability of the neuron to synthesize NE, resulting in a buildup of DA.

In 1986, we, and independently, colleagues in Rotterdam, reported a syndrome in which patients have a congenital absence of the DBH enzyme. Results of a battery of biochemical and physiological tests in DBH-deficient patients helped us to identify the pathophysiology of these patients and enabled us to design an effective treatment.

Occasionally, patients present to the Autonomic Dysfunction Center with a unique constellation of

symptoms of autonomic dysfunction so that they do not fit into a diagnostic category (Orthostatic Intolerance, Pure Autonomic Failure, Multiple System Atrophy, Baroreflex Failure). Some of these patients have severe orthostatic hypotension and resemble those with DBH deficiency, but they do not have the extreme plasma levels of DA. We propose that medication trials in these patients will assist us in optimizing their treatment. Evaluation will be undertaken under controlled conditions with medication and dietary restrictions and will consist primarily of orthostatic blood pressure and heart rate measurements and plasma catecholamine determinations.

Participants will first take part in a study designed to provide information on the pathophysiology of their autonomic problems (The Pathophysiology of Orthostatic Hypotension, IRB#030752, CRC approval pending). Results from this study will help us determine which drug(s) to administer in the proposed protocol.

PRELIMINARY STUDIES

Once the pathophysiology of DBH deficiency was understood, we were able to rapidly develop a specific and effective therapy. Consistent with DOPA and DA reducing blood pressure, the administration of a tyrosine hydroxylase inhibitor, such as metyrosine, raises blood pressure in DBH-deficient individuals. The pressor effect appears to correlate with the metyrosine-associated reduction in plasma DA and DOPA levels and also urinary DA levels. DOPS, or Droxidopa INN:(-)-threo-3-(3, 4-dihydroxyphenyl)-L-serine, is structurally closely related to NE, but has an additional COOH group. It can be pumped up into the noradrenergic nerves and converted into NE by L-aromatic amino-acid decarboxylase without requiring DBH. L-DOPS has been used effectively in the treatment of patients with complete DBH deficiency. It might also improve the blood pressure in patients that have profound orthostatic hypotension but do not appear to have complete DBH deficiency.

EXPERIMENTAL DESIGN AND METHODS

Participants in this study are patients with hypotension, who have undergone evaluation as part of our "The Pathophysiology of Orthostatic Hypotension" protocol (IRB#030752, CRC approval pending). Based on the results of these studies, we will administer medication which we believe might improve their symptoms. We will first test a single dose of one or more drugs with monitoring for 24 hours. A drug or drugs effective at preventing an orthostatic fall in blood pressure might then be tested in a 5-day crossover trial with comparison of effects to placebo. Based on the results of the 5-day trial, a patient might then be given a 2-month trial of the drug, with periodic admissions to the GCRC for assessment of symptoms. The period of time needed to complete this study will depend on the number of medications tested.

Drug withdrawal

Participants must remain off any medications that could affect blood pressure for three days prior to and during study. This includes not only their usual scheduled medications, but also other drugs that might be taken intermittently. If their symptoms are severe enough that they or their physician have concerns that their symptoms may worsen, they may be admitted to the hospital for observation during this portion of the study. While they are an inpatient on the GCRC, their general condition, blood pressure and heart rate will be checked regularly to reduce any risk.

Urine pregnancy test

We will perform a urine pregnancy test every time female participants are admitted to the hospital for this study.

Diet

We will ask study participants to eat a standard diet with no caffeine, 150-mEq/day sodium, 70 mEq potassium, and no substances that interfere with catecholamine synthesis, release or assay for three days prior to and during testing.

24-Hour Urine Collection
Participants will collect their urine for 24 hours every time they are admitted to the hospital for this study. The urine will be analyzed for sodium, potassium, creatinine,and catecholamines.

Orthostatic vital signs
Orthostatic vital signs will be measured several times a day. This testing consists of blood pressure and heart rate measured while patients are lying down and then repeated after standing quietly for 5 minutes, using the Dinamap.

Single-dose drug trials
Participants will be admitted to the Vanderbilt Clinical Research Center the evening prior to the study. In the morning, the patients will be seated or in bed for a 30 min baseline period of blood pressure and heart rate monitoring. The medication will be given by mouth, and blood pressure and heart rate will be monitored every 10-15 minutes for the first hour, using a Dinamap. Orthostatic vital signs will be taken after 1, 2, 3, 4, 8, and 12 hours. Fifteen ml of blood will be collected through a saline lock during baseline and after 2, 4, and 8 hours while in the supine and standing positions to measure catecholamines (total of 4 samples lying down and 4 samples upright). Aldosterone will also be measured in blood collected during baseline and at one other timepoint, depending on the duration of the drug effect (total of 2 samples lying down and 2 samples upright). A second blood sample will be collected with the aldosterone and an aliquot of plasma frozen for possible analysis of plasma renin activity. Urine will be collected from 0-7 hours, 7-12 hours and 12-24 hours for measurement of catecholamines. Depending on how well the drug is tolerated and the degree of improvement in orthostatic vital signs and symptoms following the drug, another single-dose drug trial might be scheduled 48 hours after the first or the patient might be asked to start a 5-day trial of the drug at that time. If they are not scheduled for another trial at this time, they can be discharged. The medications include domperidone, metyrosine, L-DOPS, alpha-methyldopa, L-dopa, carbidopa, atomoxetine, and placebo.

Single-dose trial

Time	Days 3,2 pre-study	Day 1 pre-study	Study Day							
			0 hr	1 hr	2 hr	3 hr	4 hr	8 hr	12 hr	24 hr
Drug/diet restriction	X	X	X	X	X	X	X	X	X	X
Urine collection		X	X	X	X	X	X	X	X	X
Admission to GCRC		X								
Pregnancy test		X								
Drug administration			X							
Blood sample			X				X	X	X	
Vital signs		X	X	X	X	X	X	X	X	

5-Day drug trials
Once the appropriate dose has been decided, we will conduct a single-blinded crossover trial. Depending on where they live and the severity of their symptoms, participants might be able to go home

for part of this study. However, after 4 days on the drug (or placebo), they will be admitted to the GCRC. They will be supine and NPO after midnight. In the morning, we will do a Posture Study to determine the effectiveness of the treatment. Before breakfast, we will draw 15 ml of blood while they are supine and another 15 ml after they have stood for 30 minutes to measure catecholamines and aldosterone. A second blood sample will be collected with the aldosterone and an aliquot of plasma frozen for possible analysis of plasma renin activity. We will monitor blood pressure and heart rate during this study, using a Dinamap. Standing time will be determined, and the participants will be asked about their symptoms periodically during the study. For at least three days following this testing, participants will take no medication. They will then start a 5-day regimen of the medication, if they previously took the placebo, or placebo, if they previously took the medication. They will not be told whether they are taking active drug or placebo. The Posture Study will be repeated in the GCRC after the second 5-day period.

5-day trial

Time	Day 3 pre-study	Days 1,2 pre-study	Study day 0	Study days 1,2,3			Study day 4	Study day 5	Study days 6,7		Study day 8	Study days 9,10,11			Study day 12	Study day 13
Drug/diet restriction	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine collection							X								X	
Admission to GCRC							X								X	
Pregnancy test	X															
Drug/placebo administration			X	X	X	X	X				X	X	X	X	X	
Posture study/Blood sample								X								X
Vital signs							X	X							X	X

Depending on the results of the 5-day trial, participants will be given a longterm trial of a drug. At the initiation of treatment, and after two weeks, four weeks, and eight weeks of drug, they will be evaluated by a posture study, 24-hour urine collection and assessment of their symptoms. The dose of the medication will be adjusted after two and four weeks of treatment if there has been insufficient improvement in blood pressure (able to stand with< 20 mmHg decrease in systolic blood pressure) or symptoms.

Chronic trial

Days	-3,-2	-1	0	1-10	11,12	13	14	15-24	25,26	27	28	29-52	53,54	55	56
Restrict diet	X	X	X		X	X	X		X	X	X		X	X	X
Collect urine		X				X				X				X	
Admit to GCRC		X				X				X				X	
Pregnancy test		X				X				X				X	
Take Drug			X	X	X	X	X	X	X	X	X	X	X	X	
Posture study/ Collect blood			X				X				X				X
Vital signs		X	X			X	X			X	X		X	X	X
Adjust dosage							X				X				

BIOSTATISTICS

Statistical analyses will be performed on a personal computer with the statistical package SPSS for Windows (Version 10.0, SPSS, Chicago). Some paired comparisons (Paired t-test, Wilcoxon signed-rank test, repeated measures ANOVA, Friedman ANOVA by ranks) might be needed to compare treatment responses within a subject.

Protection of Human Subjects:

POPULATION:

The conduct of these studies will involve approximately 25 human subjects. Subjects will include patients with severe orthostatic hypotension and other autonomic symptoms who do not meet criteria for one of our standard diagnoses. Potential study participants will first take part in "The Pathophysiology of Orthostatic Hypotension" (IRB #030752, CRC approval pending). Results from that study will provide information on the pathophysiology of the autonomic disorder and might suggest which medication(s) might be an effective treatment. Subjects will range in age from 18-70 and be non-smokers, drug-free, able to give informed consent, and free of pulmonary, renal, hematopoietic, hepatic and cardiac disease. Exclusion criteria for the study include smoking, pregnancy, medications affecting the autonomic nervous system, any chronic illness, and anemia (Hct<35).

RESEARCH MATERIALS:

Research materials include blood, urine, and data. The blood will be analyzed for catecholamines, renin and aldosterone. Urine will be analyzed for catecholamines, sodium, potassium, and creatinine.

RECRUITMENT OF SUBJECTS:

We will recruit patients from those referred to the physicians of the Autonomic Dysfunction Center at Vanderbilt who have participated in "The Pathophysiology of Orthostatic Hypotension" (IRB #030752, CRC approval pending). In each instance, the investigator will describe the complete protocol to the prospective participant. The subjects will then be given a written informed consent form that has been approved by the Vanderbilt Institutional Review Board. The subject will be given adequate time to read the consent form, ask questions, and if satisfied by the responses, sign the form. Consent or refusal to participate in this study will not affect medical care. No modifications or waiver of the elements of consent have been authorized, nor will any be necessary in the execution of this study.

POTENTIAL RISKS:

Blood drawing and insertion of venous catheters are uncomfortable and may cause bruising, bleeding, permanent damage to the vessel and in rare instance, infection. The risk of bleeding can be prevented by tight compression of the site. Experienced personnel will place all intravascular lines using sterile technique.

Consuming a sodium- and caffeine-controlled diet might not be to the subject's taste preferences. If a subject drinks caffeinated beverages regularly and stops caffeine intake suddenly, he/she might have headaches and fatigue for a few days. These symptoms can be avoided by cutting down gradually on the amount of caffeine in the diet.

Stopping medications might cause a temporary worsening of symptoms for patients. Careful monitoring of blood pressure and heart rate will permit immediate attention and termination of the protocol when necessary.

Collection of urine can be inconvenient.

The seated oral medical trials are tedious and boring because they require being seated for an extended period of time while blood pressure is monitored.

When any medication is used in testing, there is a small risk of an unforeseeable life-threatening allergic reaction. Side effects associated with specific medications are listed below. Side effects are listed as common, uncommon, and rare.

Domperidone – common: dry mouth, abdominal cramps, diarrhea. Uncommon: loss of balance or muscle control, swelling of mouth, increased breast milk flow, headache, hives, hot flashes. Rare: pounding or racing heart beat, swelling of extremities, change in appetite, constipation, dizziness.

α-Methyldopa – common: weakness, distention of lower abdomen, constipation, swelling of the lower extremities, fever and depression, anxiety, nightmares, being sleepy or drowsy, headache and dry mouth. Uncommon: dizziness, gas, diarrhea, chest pain, stuffiness of the nose, low blood pressure on standing, low heart rate, nausea or vomiting, abnormal liver function tests. Serious or life-threatening: extremely rare reactions are fatal liver damage and fatal inflammation to the heart.

Carbidopa – only reported to have adverse effects when it is given with the drug levodopa for Parkinson' s disease. Common adverse events with the carbidopa-levodopa combination include dyskinesias and nausea. Less common adverse effects are psychotic episodes, depression and dementia.

Metyrosine – common: drowsiness, diarrhea, drooling, trembling and shaking of hands and fingers; trouble speaking. Uncommon: decreased sexual ability in men, dry mouth, nausea, vomiting, stuffy nose, anxiety, confusion, hallucinations, mental depression. Rare or life-threatening: crystalluria (the excretion of crystals in the urine resulting in urine retention), black, tarry stools, unusual bleeding or bruising, muscle spasms, painful urination, pinpoint red spots on skin, restlessness, shortness of breath, shuffling walk, skin rash and itching, swelling of feet or lower legs, tic-like movements

L-Dopa (levodopa) – common: abdominal pain, dry mouth, loss of appetite, nightmares, gas, abnormal thoughts, agitation, anxiety, clumsiness, difficulty swallowing, dizziness, excessive watering of mouth, nausea and vomiting, uncontrolled body movements. Uncommon: Chest pain, mood or mental changes, discoloration of sweat or urine, constipation, diarrhea, flushed skin, headache, hiccups, increased sweating, muscle twitching, trouble sleeping, blurred vision, difficult urination, dilated pupils, dizziness or lightheadedness when getting up from a lying or sitting position, double vision, fast or pounding heartbeat, hot flushes, mental depression, skin rash, weight gain or loss. Rare: back or leg pain, black tarry stools, chills, convulsions, fever, high blood pressure, loss of appetite, swelling of feet or lower legs

Atomoxetine – common: headache, nausea, sleepiness, trouble sleeping, anxiety, dry mouth, loss of appetite, dizziness, constipation, flushed or warm sensation, rash. Uncommon: loose stools, excessive energy, excitement, stomache ache, fluttering sensation in chest, abnormal heart rhythm sensations, tingling, vomiting, aching muscles. Rare: abnormal blood tests, such as abnormal liver function tests

L-DOPS – The use of L-DOPS is under investigation and is not approved by the FDA. We have used it for many years in a small population of patients that lack dopamine-beta-hydroxylase, the

enzyme that converts dopamine to norepinephrine. The initial dose is low and adjusted to treat low blood pressure without adverse effects. It is possible that there may be some side effects. The following rare side effects have been reported: increased blood pressure, nausea, headache, hallucination, anorexia, increased liver enzymes, dizziness/lightheadedness, heart fluttering, thirst, nervousness, stomachache, vomiting, abdominal pain, chest pain, and fatigue.

Placebo – The placebo is a pill or capsule that does not contain active ingredient. It should therefore have no side effects.

PROTECTION:

Monitoring of vital signs will help minimize potential risks. All information will be kept strictly confidential.

BENEFITS:

We guarantee no direct benefits to the study participants. Results of this study will improve our understanding of autonomic dysfunction and might lead to important advances in the management of these diseases.

DATA SAFETY MONITORING PLAN

Data from subjects enrolled in this study will be reviewed on a bi-monthly basis by the P.I.and at least one co-investigator. Any adverse event of a serious or greater nature will be reviewed immediately with the P.I. Emily Garland, Ph.D. will be responsible for tracking adverse events in this study.

The adverse event will be described with the following information: description of the event; outcome of the event; duration of the event; relationship to study procedure; requirement, if any, for treatment or intervention; and outcome.

Adverse events will be graded according to the following scale:

0 = No adverse event or within normal limits

1 = Mild adverse event (transient and mild in nature, and no treatment is necessary)

2 = Moderate adverse event (some intervention and treatment are necessary, but participant completely recovers

3 = Severe adverse event (an event that results in hospitalization, disability, or death or is life-threatening)

The investigator will state his opinion on whether there is a reasonable possibility that the event or experience is related to a procedure performed as part of this study.

JUSTIFICATION FOR GCRC UTILIZATION

The following GCRC services are necessary for conducting this scientific study:

Inpatient/Outpatient Support: Approximately 25 patients will be studied over the five years. The length of stay and number of admissions will depend on the number of medication trials performed with each patient. A research nurse will be needed to draw blood and monitor blood pressure during pharmacological testing, to document pulse and blood pressure during orthostatic vital signs, to perform posture studies, and to assist with urine collections, as well as for general patient care.

Biostatistical Support: Although we do not anticipate doing any data analysis, review by the GCRC biostatistician is requested, as well as assistance with any unforeseen data analysis.

Informatics Support: Review by the Informatics specialist and access to data from the Core Lab is required.

Core Lab Utilization: The Core Lab is needed for plasma and urine catecholamine analysis and urinary sodium, potassium and creatinine.

Nursing Support: Nursing support will be needed for blood draws, urine collections, posture studies, and medication studies.

Nutrition Services Utilization: We will ask patients to eat a standard diet with no caffeine and 150 mEq sodium, 70 mEq potassium while in the hospital for these procedures. We might ask them to restrict their diet for up to three days prior to admission.

OTHER SUPPORT

84 urine pregnancy tests are needed.
700 plasma aldosterone and 50 plasma renin analyses are requested, as well as processing of 650 aliquots of plasma to be frozen for possible future analysis of plasma renin activity.

Gender/Minority Mix

This study does not exclude research participants by race or gender and includes research participants aged 18 – 70 years old. We expect the overall distribution of participants to be even across gender and ethnic groups.

Table I – National Figures for Mix of Study Population

	Am. Indian Alaskan Native	Asian Pacific Islander	Black, of H Origin	Hispanic	White, of H Origin	Other	Total
Male	0.4	1.4	5.7	4.3	36.9	*	48.7
Female	0.4	1.4	6.0	4.5	38.8	*	51.1
Total	0.8	2.8	11.7	8.8	75.7	*	99.8

* negligible in this context. Note: Rounding errors led to totals different from 100%.

Table II – Tennessee Figures for Mix of Study Population

	Am. Indian Alaskan Native	Asian Pacific Islander	Black, of H Origin	Hispanic	White, of H Origin	Other	Total
Male	0.1	0.5	7.4	0.4	39.9	*	48.3
Female	0.1	0.5	8.0	0.4	42.8	*	51.8
Total	0.2	1.0	15.4	0.8	82.7	*	100.1

* negligible in this context. Note: Rounding errors led to totals different from 100%.

Table III – Anticipated Enrollment – Actual Patient Numbers

	Am. Indian Alaskan Native	Asian Pacific Islander	Black, of H Origin	Hispanic	White, of H Origin	Other	Total
Male	0	0	2	1	10	0	13
Female	0	0	2	0	10	0	12
Total	0	0	4	1	20	0	25

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