

Consent Form for Participation in Research

New York Medical College

Affiliate:

Name of Patient/Subject :

Address:

Chart Number:

Title of Research Project: *Circulatory Dysfunction in the Chronic Fatigue Syndrome*

Note:

This project does not involve the experimental use of a new drug/device/procedure.

Explanation of Research Project:

Purpose of the Study

You are being asked to participate in research to determine whether the regulation of blood pressure and blood flow cause the symptoms of chronic fatigue syndrome (CFS) and whether treatment of abnormal blood pressure and blood flow improves these symptoms. Evidence suggests that patients with CFS can have symptoms along with abnormal blood flow when they are kept upright. Adolescents, in particular, develop high heart rates often associated with low blood pressure along with symptoms such as light-headedness, mental confusion, sweats and palpitations. Our research suggests that this is due to alterations in the function of blood vessels particularly causing fluid to be trapped or “pooled” in the lower parts of the body. This can sometimes show up as swelling when blood is trapped in muscle or purple discoloration of the legs when blood is trapped in the skin. Pooling leads to decreased blood returning to the heart which becomes unavailable to be pumped. This in turn stresses the nervous system. The purpose of the study is to determine the precise way that blood vessels malfunction and to learn whether improvement in blood vessel function with medication can improve pooling and also the way that the nervous system functions.

Participation

If you decide to participate we will compare information from patients with CFS to information from healthy volunteers. During screening, we will ask questions to determine whether you have CFS. A physical examination will be performed to look for heart disease and neurologic disease. We will also ask you to fill out a questionnaire which relates to symptoms of the syndrome, to fainting problems, and to your general state of health. Laboratory blood tests may have been performed to rule out thyroid disease, liver disease and anemia. If you are a woman and are willing to participate, we will also need you to obtain a test to ensure that you are not pregnant.

All subjects - CFS and healthy volunteers - will undergo accepted tests of the ANS

These are performed in a laboratory with an intravenous catheter (an IV) in place while being continuously monitored for blood pressure, breathing rate and heart rate:

- 1) tests of “heart rate and blood pressure variability” at rest and while upright. This test measures changes in the way heart rate and blood pressure are regulated by recording heart beat and blood pressure for a period of time and analyzing those recordings.
- 2) determination of the blood pressure and heart rate response to the quantitative Valsalva maneuver. This maneuver is performed by blowing against a pressure for approximately 10 seconds.
- 3) determination of blood pressure and heart rate responses to deep breathing in time to a metronome.
- 4) head-up tilt table testing, a routine test which is used to evaluate patients with CFS or fainting. Patients are placed on an electrically driven table with supporting footboard capable of tilting upright. Patients are gradually tilted upright in steps from flat to 20°, 35°, and 70°. During the 20° and 35° tilts

we will make measurements of blood flow (see below) and take small blood samples for hormone levels.

All patients will also undergo tests of how the blood vessels function:

- 1) strain gauge venous plethysmography which measures leg and arm vein filling using a strain gauge (an elastic band) encircling the limb and detects changes in fluid within the limb caused by rapidly inflating a blood pressure cuff. Plethysmography will be performed in the arm and the leg while lying flat, and during the tilt tests.
- 2) impedance plethysmography which uses pairs of electrocardiogram stickers to measure small changes in voltage on passing a tiny current (similar to an electrocardiogram). The voltages tell us whether blood volume is increasing or decreasing and also information about blood flow.
- 3) transcranial Doppler ultrasound which uses sound waves to measure the amount of blood flow to the brain. The sensor will be placed at the left temple of the head.
- 4) cardiogreen dye dilution which is a technique to measure the total body blood volume and blood flow by introducing a small amount of dye into a vein and measuring the amount of color change through a noninvasive finger sensor.
- 5) Evans blue dye dilution technique may be used as an alternative to cardiogreen if the latter is unavailable. The technique is also used to measure blood volume by introducing a small amount of dye into a vein but requires sampling from the vein as well.
- 6) laser-Doppler flowmetry will be used to measure skin blood flow while lying flat and during tilt tests. A laser light similar to a laser pointer will be attached to the skin. While flat we will also be able to tell how well nerves are working by administering tiny amounts of medication to a small area of skin while continuing to measure flow. This technique is called iontophoresis. There are no effects to your system from these medications. We make measurements only to the area of skin that receives the medication.

Treatment of CFS Patients

CFS patients only will receive a test of treatment over two 2 week periods with one week in between (a total of 5 weeks). All CFS patients will receive a single oral treatment of proamatin (midodrine), a medication that contracts blood vessels and is used to treat patients with low blood pressure and lightheadedness. Patients will also receive placebo which is a substance with no medicinal value (like a sugar pill). Patients will be assigned to take proamatin or placebo in random order (by the flip of a coin) and neither the patient nor the doctors will know which is which - this is called double-blind testing. The pharmacy will know. After initial testing, patients will receive the first medication for 2 weeks and then be retested with questionnaires, blood vessel function test and low angle 35° tilt testing. All treatments will stop (called a “washout period”) for 5 days. Patients will start the second medication and testing repeated after another 2 weeks.

Test sessions will last approximately 3 hours.

Risks and discomforts

Monitoring, plethysmography, laser-Doppler flowmetry and transcranial Doppler ultrasound are painless and contribute no additional risk to your care. Iontophoresis has not been associated with any adverse events. To date there have been no reported adverse effects from the small doses of agents to be given transcutaneously. There is no foreseeable risk to performing the Valsalva maneuver or deep breathing. Cardiogreen or Evans blue dye will be administered intravenously. These have no chemical effects and have no direct effects to your system. Should there be any sign of an allergic response such as rash, wheezing, or a decrease in blood pressure, administration of the dye will stop and counter measures taken.

Tilt testing is intended to replicate fainting or pre-fainting symptoms which constitute its primary risk. Tilt testing is, however, the standard for assessing patients with unexplained fainting and also has become standard in the assessment of patients with CFS. Low angle tilts to 20°, and 35° have been well tolerated by a pilot group of CFS patients and healthy volunteers. High angle tilts to 70° have been used in a pilot group of patients and healthy control subjects and can sometimes provoke fainting. Physical

risks will be minimized by returning patients who faint or nearly faint promptly to the back-down position. Intravenous fluids can be given if needed at the end of the tilt test and invariably improve overall well-being after fainting. In recent testing neither CFS patients nor volunteers have actually fainted.

Blood drawing risks (during screening laboratory evaluations) include pain from the needle stick and bruising.

Proamatine is a medication which contracts blood vessels and therefore can cause high blood pressure in sufficiently large doses. This is uncommon in CFS patients whom we have treated. Blood pressure will be home monitored with medication change throughout the treatment phase and the medication adjusted or stopped as necessary. Other side effects such as itchy feelings, or a pins and needles sensation are usually short-lived or may call for a decrease in dose if persistent. Worsening CFS symptoms could occur as well. We will monitor patients for these possibilities over the course of the study and alter medication if necessary.

Benefits

There may be direct benefit from this study to patients with blood vessel function and associated abnormalities of the ANS especially if proamatine improves their function. You may therefore derive immediate benefit from the study because it may directly improve your health. Also the study will enable us to detect changes in blood vessel function which may furnish data important for determining other suitable medical therapy in CFS patients. There is no direct benefit to healthy volunteers, although their contribution is essential for purposes of experimental control. Healthy patients will contribute to general medical knowledge.

Alternatives to participation

The alternative is standard medical care.

Payments and compensation

\$200 per subject.

Additional information

There will be no additional cost for testing or medication to the patients. Significant new findings which may relate to your willingness to continue participation will be provided. Any worsening in clinical status detected during monitoring and testing will be promptly treated using standard therapeutic regimens. Over a four year period we expect to enroll 50 patients with CFS, and 30 healthy volunteers.

All inquiries will be promptly answered by contacting either of the investigators Julian M. Stewart M.D., Ph.D. (914-594-4370)

