PROTOCOL OF EXPERIMENT INVOLVING HUMAN VOLUNTEERS

Title: The Use of Chlorothiazide Under Simulated Flying Conditions.

Project: 7755-02-001.

Principle Investigators: Major John H. Triebwasser, Major Malcolm C. Lancaster, Captain Carol Corrado, Captain David Smith, Lt Fred Shank, Dr. Bryce Hartman, Major William K. Brown, Captain George Cohen, Captain Chandler Cheek, and Dr. Sidney D. Leverett.

Medical Consultant: Colonel Timothy N. Caris

Technical Objectives: Hypertension is a problem of considerable magnitude in the flying population. The majority of the hypertensive pilots that are allowed to remain on flying status, have blood pressure elevations that are presently considered to be of a magnitude not requiring the administration of medications. Recent work would indicate early treatment to be a benefit to prevent vascular complications. Any form of drug therapy would necessarily imply suspension from flying duties. Chlorothiazide is a drug with a low incidence of side effects, that will lower the blood pressure in those individuals with diastolic pressures less than 110 mm Hg (this range is that found in all of the hypertensive pilots allowed to remain on flying status). The purpose of this experiment is to administer chlorothiazide to human volunteers and observe their psychomotor performance and physiologic responses under simulated flying conditions.

Background: Chlorothiazide, a benzothiadiazine derivative, is a potent diuretic agent that lowers the blood pressure independent of changes in the blood volume. It works on both the proximal and distal renal tubules resulting in an increased urine volume containing increased quantities of sodium and potassium. Within 48 to 72 hours, the plasma volume and the total extracellular water are decreased maximally, possibly at the expense of intracellular water. Physical endurance is decreased at this stage, but becomes normal after correcting the reduced plasma volume with dextran. To date no work has been done to study the effect of this medication on tolerance to $+G_z$ forces in a rotating human centrifuge. Within 4 to 5 weeks of continuous treatment, the plasma volume is normal. The extra and intracellular fluid volume returns to normal within 8 to 12 months while continuing the medication.

The blood pressure lowering effect is independent of the above. The peripheral vascular resistance is lowered without any change in the cardiac output or blood volume. Many hypothesis have been published including reduction of tissue pressure, alterations in electrolyte content of the arterioles, blocking norepinephrine's action on the arteriole, and alterations in trace element metabolism. None of these postulates have been proven.

This drug has been proven to be quite safe as reflected by its continual usage over the past 10 years. Hypokalemia and its consequences is the most important side effect. Its occurrence is thought due to the drugs action directly on the tubules and secondary increased production of aldosterone. However, this is of little importance if the diet contains adequate potassium and sodium.

There have been isolated reports of hyperglycemia early in the course of treatment with this medication. This occurs primarily in individuals who are prone to develop diabetes, i.e. positive family history and/or abnormal glucose tolerance tests. The reasons for this are not clear. Evidence to date would suggest that chlorothiazide interfers with glucose utilization in the periphery by several possible mechanisms. More work needs to be done to further delineate this aberration.

Chlorothiazide will elevate the blood uric acid to a slight degree. This has not been a problem except in those individuals who have gout.

There have been isolated reports of skin rashes, agranulocytosis, thrombocytopenia, cholestatic jaundice and pancreatitis.

Hazards: The potential hazards to the subjects are minimal. They will be subjected to standard stress tests including maximum treadmill exercise, lower body negative pressure, positive G_z angular acceleration, and exposure to a 12,000 foot altitude, breathing ambient air, and 18,000 feet, breathing 100% oxygen by mask in the altitude chamber. These tests have been utilized in the past here at the School of Aerospace Medicine with essentially little difficulty.

The total radiation exposure will be approximately 40 milli rads over the 12 weeks of the experiment.

Hazardous duty pay will be requested in accordance with Chapter 5, AFM 177-105 during the 12 weeks of the proposed experiment.

Requirements for Human Volunteers:

a. Number Required: Approximately three groups each containing 6 subjects will be studied. The observations made with the first two groups (16 subjects) will dictate future requirements.

b. Date and Total Number of Days Required, Including Convalescent Leave: The first group studied should arrive on or about 15 June 1968. The second group will be studied beginning 6 January 1969. The third group should begin on 5 May 1969. Each subject will be on Brooks Air Force Base for a period of 12 weeks, followed by a two week convalescent leave (Note attached outline).

c. Schedule of Experiment: There will be a two weeks control period, 8 weeks of study while ingesting 1 gram of chlorothiazide per day, followed by a 2 week recovery period. The first group will be housed on the metabolic unit where a carefully controlled metabolic balance study will be performed throughout the 12 weeks of the experiment. Subsequent groups will be housed in the airman's dormitory and fed in the airman's dining facilities.

Clinical testing will include an initial and final Class II flying physical examination, chest and sinus x-rays, and electrocardiograms.

They will be subjected to weekly treadmill exercise and lower body negative pressure stress testing. Psychomotor tests will be administered daily. During the 1st through 4th, 8th, and 10th through 12th weeks of the study, all will be subjected to positive G_z acceleration on the human centrifuge until blackout occurs (visual loss). During the 6th and 7th weeks (Monday thru Friday) psychomotor tests will be administered in the altitude chamber under simulated flying conditions. One-half will be exposed four hours daily to a 12,000 foot altitude breathing ambient air and the remainder to 18,000 feet, breathing 100% oxygen via masks.

Metabolic balance studies (in the 1st group) will include analysis of food, water, urine and stool for electrolytes including trace elements, nitrogen, calcium, and phosphorus. Creatinine and uric acid clearances and urinary catecholamines will be determined weekly.

Hematological studies (other than the isotope procedures listed below), blood chemistries, and liver function studies will be determined weekly.

Red cell mass using Cr^{51} labeled red blood cells and plasma volume using I^{125}-labeled albumin, will be determined during the second, third, seventh, and eleventh weeks. Total body water will be measured during these times using the deuterium dilution method.

Glucose tolerance tests including plasma insulin determinations will be performed during the 2nd, 7th and 12th weeks of the study.

Those individuals studied on the metabolic unit will be supervised 24 hours a day by a medical technician.

d. Duties and Procedures to be Performed by Human Volunteers: No further duties are planned other than to help police the ward during the experiment.

e. Special Requirements: The volunteers will be obtained from the Lackland Air Training Command and will have just completed basic training. They shall be between the ages of 18 through 25 years and will be selected on the basis of a negative history and physical examination for cardiovascular, metabolic, and musculoskeletal diseases. There are no special intellectual or educational requirements.

f. Prior Screening Required: During the initial interview, all potential candidates will undergo psychological testing in an attempt to obtain cooperative, emotionally stable subjects for each group.

Potential Dangers to Human Volunteers/Safety Measures: The potential hazards were listed above. All laboratory personnel will wear film badges and the laboratories will be monitored weekly. Disposal of waste products will be conducted in accordance with procedures outlined by the Radiology Branch.

During exposure to the maximum treadmill exercise, lower body negative pressure, and acceleration stress tests, a physician will be in attendance at all times and will interrupt the procedure if there is evidence for a dysrhythmia or any other complications. Appropriate resuscitative equipment will be available for immediate use at all times.

All the subjects will be informed as to the amount of radiation they will receive as well as other potential hazards prior to obtaining written consent. They will also be informed that they can withdraw from the experiment at any time.

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