7/2/73

Ø388

D-72

THE EFFECTS OF PERHEXILINE MALEATE UPON REGIONAL MYOCARDIAL PERFUSION AND THE EXTENT OF TRANSIENT MYOCARDIAL ISCHEMIA AS ASSESSED BY POTASSIUM-43 MYOCARDIAL PERFUSION IMAGING

AIR1 941130 064cc

INVESTIGATORS

Barry L. Zaret, Major, USAF, MC (as of September 1973, Assistant Professor of Medicine, Yale University School of Medicine)

M. D. Flamm, Jr., Lt. Colonel, USAF, MC

Neil D. Martin, Colonel, USAF, MC

OBJECTIVE

To assess the effects of perhexiline maleate upon regional myocardial perfusion and exercise-induced transient myocardial ischemia in patients with typical angina pectoris.

PATIENT SELECTION

The initial study group will be comprised of 10 patients with angina pectoris due to coronary atherosclerosis. The angina pectoris will be documented by a careful history, which should agree closely with Heberden's clinical description, particularly as to location and character of the pain itself. The angina should be stable for at least 6 months.

The coronary atherosclerosis will be documented by coronary angiogram in at least one-half of the patients and by a positive exercise tolerance study in all of the patients.

APPROVED
EM
7-3-73

6385

Patients will be screened with maximal treadmill exercise tests and will be included only if ischemic chest pain occurs during testing and is associated with ischemic ST-segment changes defined by at least 1 mm. of flat or downsloping ST-segment depression lasting at least 0.08 seconds in 3 consecutive beats in a lead with a normal control configuration.

Patients with a previous myocardial infarction (MI) may be included provided there is a measurable difference between their resting and exercise potassium-43 myocardial perfusion scans. The MI should be at least 6 months old.

Patients in whom there is a possibility of pregnancy will be excluded from the study.

The experimental nature of the study will be explained to each patient and informed consent obtained. The final number of patients studied is dependent upon analysis of the initial study group, and it may become necessary to include an additional 10 patients.

POTASSIUM-43 MYOCARDIAL PERFUSION SCANNING

The technique, which was developed at David Grant USAF Medical Center, allows the imaging of the left ventricular myocardium both at rest and during the stress of maximal treadmill exercise. Potassium-43 when administered intravenously distributes in the left ventricle in proportion to both the regional coronary blood flow and the integrity of regional cell membrane function with respect to active cation transport. We have

0358

demonstrated the appearance of reproducible abnormalities in myocardial images obtained on a rectilinear scanner following injection of potassium-43 during exercise-induced angina pectoris. Images in the same patients obtained at rest are either normal or show significantly less abnormality. These abnormal regions of the left ventricular image correspond to zones supplied by angiographically demonstrable stenotic major coronary arteries. These regions have involved from 17 to 54% of the left ventricular image in the anterior view. Current experience includes 129 studies in 72 patients. Preliminary reports of this technique have been presented at several scientific meetings. An initial report of this technique in patients with coronary atherosclerosis is currently in press.

PROCEDURE

This will be a double-blind crossover, randomized study. During the screening period, each patient will undergo control graded maximal exercise testing to the end point of ischemic chest pain. Studies will be performed with a multi-lead electrode system and a motorized treadmill; a standard Bruce protocol will be followed. Each patient will then undergo control potassium-43 myocardial scanning at rest and again at the point of exercise-induced angina pectoris. Patients included in the study will have an abnormal scan after exercise when compared to the resting scan. Blood pressure and heart rate will be monitored during exercise and appropriate rate-pressure products tabulated. Enough treadmill testing will be done to establish a baseline exercise tolerance for each patient.

0388

As patients enter the study they will be given either perhexiline 400 mg. daily (200 mg. tabs b.i.d.) or an identical appearing placebo, by random distribution. The same treatment will be continued for 8 weeks. At 7 weeks into therapy patients will be exercised on the treadmill to their baseline heart rate. At this time a potassium-43 scan will be done and blood pressure and heart rate levels will be recorded. After 8 weeks of therapy patients will be exercised to the point of angina pectoris, or through the entire exercise treadmill protocol, when a potassium-43 scan will again be done along with a recording of heart rate and blood pressure.

After the 8 weeks of therapy, medication will be discontinued for 4 weeks. During the fourth week patients will again be tested on the treadmill to the point of angina pectoris in order to establish a new baseline heart rate. A potassium-43 scan will be done after the exercise testing. Medication will then be instituted and will be the opposite one received during the first 8-week period. Exercise testing and myocardial scanning with potassium-43 will be done as before after 7 and 8 weeks of continuous therapy. The exercise at 7 weeks will be at the second baseline heart rate value and at 8 weeks will be at maximum level.

Prior to the time that a potassium-43 scan (after exercise) is done at weeks -1, 7, 12, and 13, a 10-ml. blood sample with EDTA as anticoagulant will be drawn. Plasma will be separated from packed cells and the frozen plasma will be shipped to the Drug Metabolism Department of Merrell-National Laboratories. A urine sample (more than 100 ml.) will be collected at the

same time and shipped frozen to the Drug Metabolism Department for analysis of metabolites of perhexiline to confirm drug regimen compliance and adequacy of the washout during the interim period. Only unwaxed containers will be used.

Laboratory work consisting of a complete blood count, urinalysis and SMA 12-60, which will include SGOT, LDH and alkaline phosphatase, will be done at the start of the study and at the end of each 8 week study period. A resting ECG will be done at the beginning and end of the study and an exercise ECG will be done with each treadmill test.

Concomitant medication will be listed prior to the start of the study and either discontinued before starting on the test drug or kept at the same dosage throughout the study.

METHOD OF REPORTING DATA

Case report forms will be designed and supplied to the investigator by the Medical Research Department of Merrell-National Laboratories. These will consist of:

1. An alert form to be completed and sent in as each patient enters the study.
2. A 2-page narrative history form which will focus mainly on heart symptoms. It will also include a question on alcohol consumption.
3. A cardiovascular system examination from which, along with the narrative history, is to be filled out and returned to the Merrell monitor as each patient enters the study.

0388

4. An 8-week evaluation form which is to be filled out at the end of each 8 weeks drug period. It will then be sent directly to the Merrell monitor.

5. ECG's resting and exercise, laboratory work, myocardial perfusion scans will be submitted to the Merrell monitor on appropriate forms.

DATA ANALYSIS

The basic statistical analysis will be done using a crossover design with each patient serving as his own control with respect to the observations during placebo and drug study periods. The variables of interest will include the exercise parameters:

1. Heart rate at which pain or fatigue occured
2. Blood pressure at which pain or fatigue occured
3. Rate pressure product at which pain or fatigue occured
4. Duration of exercise

and for potassium-43 myocardial image:

1. Presence or absence of ischemic left ventricular regions
2. Extent and location of ischemic zones during exercise.

Additional analysis utilyning baseline or control information will be done if so indicated. Other comparisons as needed for the above or other variables to further elucidate and evaluate the results from this study will also be done.

STUDY OUTLINE

	SCREENING EVALUATION		FIRST Rx PERIOD								INTERIM (NO THERAPY)				SECOND Rx PERIOD							
WEEK	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Alert form sent in		X																				
History & Physical		X																				
Exercise Treadmill & ECG	X	X							X	X				X							X	X
Potassium-43 Scan																						
1) at rest	X																					
2) after exercise		X							X	X				X							X	X
Laboratory (CBC, SMA-12, Urinalysis)		X																				X
Frozen Plasma Sample		X							X					X							X	
Frozen Urine Sample (>100 ml.)		X							X					X							X	
Resting ECG		X																				X
Evaluation Form										X												X

E
7-3-93

E380