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DEPARTMENT OF THE AIR FORCE
DAVID GRANT USAF MEDICAL CENTER (MAC)
TRAVIS AIR FORCE BASE, CALIFORNIA 94535



REPLY TO
ATTN OF

SGE/2573

18 September 1975

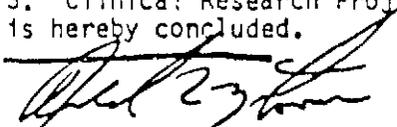
SUBJECT

Final Report on Clinical Investigation Research Project #500: The Effects of Perhexiline Maleate Upon Regional Myocardial Perfusion

TO

SG

1. Please find attached the clinical research report on The Effects of Perhexiline Maleate Upon Regional Myocardial Perfusion and the Extent of Transient Myocardial Ischemia as Assessed by Potassium-43 Myocardial Perfusion Imaging. This project was completed July 1975 and the final formal report is submitted in accordance with AFR 169-6. The final conclusions are outlined briefly in the summary, page 10.
2. A copy of this same report has been forwarded to Merrell-National Laboratories, Cardiovascular Clinical Research Division, and an abstract of the results will be published in the October 1975 Supplement of the American Heart Association Journal, Circulation. Approval for the publication has been granted by MAC/SGP.
3. Clinical Research Project No. 500, David Grant USAF Medical Center, is hereby concluded.


 RONALD L. MCGOWAN, Colonel, USAF, MC
 Cardiologist

1 Atch
Final Rpt, Clinical Research
Project #500

1st Ind

Cy to: MAC/SG
HQ AMD/RD

David Grant USAF Medical Center/SG

TO: HQ USAF/SGPR

AIR1 941130 064h

Forwarded for your information.


 MONTE B. MILLER, Colonel, USAF, MC
 Commander

0388

CLINICAL RESEARCH REPORT

ON

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

INVESTIGATORS

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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 was comprised of 10 patients with angina pectoris
due to coronary atherosclerosis. (Attachment I) The angina pectoris was
defined by a careful history, which agreed closely with Heberden's clinical
description, particularly as to location and character of the pain itself.
In every case angina was stable for at least 6 months prior to entry into
the study. None of the patients had evidence for a prior myocardial in-
farction. Patients were screened with maximal treadmill exercise tests.

according to the Bruce protocol to angina pectoris associated with ischemic ST-segment changes defined by at least 1 mm of flat or down-sloping ST-segment depression lasting at least 0.08 seconds in 3 consecutive leads in a lead with a normal control configuration. The patients ranged in age from 38 to 56 years and included 9 males and one post-menopausal female. For personal reasons, one male patient was not able to complete the second half of the protocol and, therefore, was dropped from the study, reducing the investigational group to nine.

This study conformed to the Declaration of Helsinki and had the approval of the institutional review committee of the David Grant USAF Medical Center and the Office of the Surgeon General, United States Air Force. The experimental nature of the study was explained to each patient and informed consent obtained.

PROCEDURE

This was a double-blind crossover, randomized study. (Attachment II). During the screening period, each patient was subjected to a graded maximal exercise testing to the end point of angina pectoris. Studies were performed with a multi-lead electrode system and a motorized treadmill adhering to a standard Bruce protocol. Each patient was subjected to control potassium-43 myocardial imaging at rest and with exercise-induced angina pectoris. *All patients included in this study manifest an abnormal myocardial scan after exercise when compared to a normal resting scan. Blood pressure and heart rate were monitored during exercise and appropriate rate-pressure products tabulated. Sufficient treadmill testing was performed to clearly establish a baseline exercise tolerance for each patient.

*See footnote Table II.

As patients entered the study they were given either perhexiline 400 mg daily (200 mg tabs b.i.d.) or an identical appearing placebo, by random distribution. The drug was packaged in bottles of 60 tablets with tear-off Chinese labels. Patients were given a 4-week supply at each visit and treatment continued for 7 to 8 weeks. Patients were clinically evaluated at 4 weeks and a clinical assessment form filled out. At 7 weeks into therapy patients were once again subjected to a graded maximal exercise test establishing a pulse-pressure product and an exercise myocardial perfusion scan. If the maximal pulse pressure product during this exercise test was more than 10% greater than that of the screening period, another exercise test was performed at 8 weeks into therapy with an end point of the pulse pressure product obtained during the screening period.

After the 8 weeks of therapy, medication was discontinued for 4 weeks. During the fourth week patients were again tested on the treadmill to the point of angina pectoris in order to establish a new baseline heart rate. A potassium-43 scan was performed in conjunction with the exercise testing. The laboratory tests were repeated and a clinical evaluation form filled out. Medication was then instituted utilizing the alternate therapy to that received during the first 8-week period. Patients were again evaluated at 4 weeks (week 16) and exercise testing and myocardial scanning with potassium-43 accomplished after 7 and 8 weeks of continuous therapy, according to the same program used during the first period of drug therapy.

Prior to the time that each exercise potassium-43 scan was accomplished at weeks -1, 7, 12 and 19, a 10-ml blood sample with EDTA as anticoagulant

will be drawn. Plasma was separated from packed cells and the frozen plasma shipped to the Drug Metabolism Department of Merrell-National Laboratories. A urine sample (more than 100 ml) was 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. Laboratory work consisting of a complete blood count, urinalysis and SMA 12-60, which included SGOT, LDH and alkaline phosphatase was accomplished at the start of the study and at the end of each 8 week study period. A resting ECG was obtained at the beginning and end of the study.

Concomitant medication was noted 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.

Subjective and semi-quantitative analysis was applied to the results of myocardial imaging using potassium-43 and a rectilinear scanner. All scan interpretations were accomplished by three qualified observers. At no time were these observers informed of the clinical or therapeutic status of the volunteers, although they were aware that the scans had been obtained on patients engaged in the perhexiline protocol. Each individual study was presented for interpretation in a coded folder. Without any other associated data available, regions of abnormal tracer uptake were identified utilizing both image projections. Then, using only the LAO images, the outer margin of the left ventricle was identified and outlined with a crayon. Similarly, any region of reduced tracer uptake, including the left ventricular cavity, was identified and outlined. A fourth

Investigator then planed both the area of the ventricle and the defect. A ratio of the regional defect area to the left ventricular area was calculated and recorded.

After erasure of crayon outlines the scans were reinterpreted and the outlines redrawn by the same observers. On this second review the scans were grouped by patient and studies identified as rest or exercise to allow comparison of regional defects. The clinical and therapeutic status at the time of accomplishing the exercise scans remained unknown. Once again the defect to total image area ratios were calculated. The observers also subjectively evaluated the exercise scans for any change in regional defect between individual studies on the same patient. All scans with defects and left ventricular outlines demarked by crayon were recorded photographically for reference.

Statistical analysis of data obtained from this study was accomplished utilizing two way variance on a Wang Model 2200 computer, the parameters analyzed included the following:

1. Duration of exercise, heart rate, blood pressure, and pulse pressure product at the occurrence of angina pectoris and ischemic ST-segment changes.
2. Duration of exercise, heart rate, blood pressure, and pulse pressure product at maximal exercise.
3. Differences between the rest scan defect ratio and the control period exercise scan defect ratio.
4. Difference between all exercise scan defect ratios on the same patient excluding those obtained during the perhexiline period.

- 5. Difference between the exercise scan defect ratios during the control period and the placebo period.
- 6. Difference between the exercise scan defect ratios during the control period and the perhexiline period.
- 7. Difference between the change in exercise scan defect size observed during the perhexiline period with that observed during the placebo period.

RESULTS

SUBJECTIVE CHANGES IN SYMPTOMS:

Six of the nine patients noted symptomatic improvement while taking perhexiline. The frequency of anginal episodes was reduced by at least half in these six patients and as a result they were able to correctly predict the perhexiline period upon completion of the study. One patient noted no significant change in symptoms between the placebo and perhexiline periods. Two patients manifest some increase in frequency of anginal episodes during the perhexiline period. Of interest is the one patient who not only manifest significant relief of his angina pectoris, but also noted a complete absence of previously experienced palpitations known to be related to ventricular premature contractions.

Four patients manifest undesirable side effects while taking perhexiline. Two patients experienced nausea, one of whom had occasional vertigo. With reduced dosage, these symptoms cleared and both had significant improvement in their anginal pattern. One patient experienced progressive symptoms of nausea, lightheadedness, weakness, and ataxia during the final two weeks of perhexiline therapy which he did not report.

to the investigators until this period was completed. This patient also manifest a significant elevation of SGOT. These untoward effects of perhexiline cleared within 3 days after cessation of therapy. This patient also felt that his angina worsened during the perhexiline period. The fourth patient experienced severe nausea, weakness and finally, vomiting., resulting in reduction of her dosage to one fourth the standard dose to reduce her untoward symptoms. She did not experience any significant benefit in her angina control at this reduced dosage level.

EXERCISE TOLERANCE TESTING:

None of the nine patients demonstrated a statistically significant change in any of the parameters measured when comparing exercise tolerance testing during the perhexiline period with exercise tolerance testing during the control and placebo periods. These parameters included duration of exercise, heart rate, blood pressure and pulse pressure product at onset of angina pectoris and ischemic ST change on ECG. There was also no change in maximal exercise tolerance as measured by these same parameters. (Attachment III)

MYOCARDIAL PERFUSION SCANNING WITH POTASSIUM-43.

All rest scans were normal and those obtained with exercise defined regional defects conforming to the vascular bed in the distribution of one or more major coronary arteries. The results of the scan interpretations when assessed individually in a noncomparative fashion, were entirely unsatisfactory. The wide scatter of regional defect to total myocardial image ratios, when plotting the decoded serial studies on each patient, made this technique unacceptable. When each exercise scan was compared with that patient's rest scan, there was in all cases a difference

of 50% or greater in the defect to total scan ratio which is statistically significant ($p < .001$). There was no statistical difference between the scan ratios obtained when comparing the rest scan to the screening period exercise scan and the rest scan to the interim period exercise scan. This technique was therefore considered sufficiently reproducible to assess the effects of perhexiline and placebo on the size of exercise induced regional image defects. When evaluated in this fashion there was no significant difference between the screening and interim exercise scan ratios and the perhexiline period exercise scan ratios. There was no significant difference when comparing these same control period exercise scan ratios with the exercise scan ratios during the placebo period. Thus, by quantitative analysis of defect size, no significant change could be established between control periods, placebo periods, and periods of perhexiline therapy. In addition, none of the observers could define any qualitative changes when subjectively comparing the serial studies on any of the nine subjects.

DISCUSSION

Previous studies have demonstrated beneficial effects of perhexiline in the treatment of patients with coronary artery disease. Subjectively, six of the nine patients in this group experienced a reduction in frequency of anginal attacks and a sense of well being. In addition, one patient noted an absence of previously troublesome palpitations, felt to be related to PVC's, while on perhexiline therapy. The remaining three patients reported no benefit during the perhexiline period and two of these had side effects sufficiently severe to warrant discontinuation of

therapy. Two patients with symptomatic improvement also experienced untoward side effect, but these cleared with a reduction in perhexiline therapy without alteration of the therapeutic benefit. No significant laboratory abnormalities were encountered other than the temporary elevation of SGOT in a patient with severe toxic symptoms.

In contrast to the subjective improvements noted, the more objective parameters were disappointing. The heart rate, blood pressure and pulse pressure product at time of onset of angina pectoris and ischemic ST depression were not appreciably altered by perhexiline. Maximal exercise tolerance was not improved. The planed areas of exercise induced myocardial perfusion scan defects were not significantly changed when comparing studies obtained during perhexiline, placebo and control periods. Although the completely blinded individual study analysis consistently localized areas of exercise induced ischemia, this method did not permit quantification of relative defect size. Because of the inability of the observers to correctly determine the extent of the defect, left ventricular cavity and myocardial outline in the exercise images without direct comparison with each patients resting image, a wide variance between the exercise defect ratios on the same subject rendered this technique unacceptable for the determination of possible perhexiline effect. When the exercise images were subjected to individual reanalysis and comparison with that patient's rest images permitted, scan ratios obtained during the control and placebo periods varied with an acceptable standard deviation of .047. With this method of data analysis a scan ratio difference of .094 between exercise studies on the same patient to a constant pulse pressure product would yield a significant change in area

($p < .05$). None of the subjects demonstrated a significant change by this method. Unfortunately, the resolution of the scanner does not permit recognition of changes in area less than 2 cm^2 when imaging the myocardium with ^{43}K and changes may well have been less than detectable. Perhaps changes in relative count rates between ischemic and normally perfused regions may have permitted recognition of more subtle benefits of perhexiline therapy, but such analysis is beyond the capability of our existing equipment.

SUMMARY

Myocardial imaging consistently identified areas of ischemia in these patients with angina pectoris. Blinded interpretation showed the ability of trained observers to accurately define the area of exercise induced defects in the same patient when stressed to a constant pulse pressure product. Although perhexiline did not favorably effect the myocardial scan or other measures of exercise induced ischemia, it did subjectively reduce the frequency of anginal episodes by at least 50% in six of the nine subjects completing this protocol.

Table I

PERHEXILENE PATIENTS
 Duration Stable Angina
 Angiography
 Concomitant Therapy

Patient	Age	Sex	Duration Stable Angina	Angiography	Concomitant Therapy
Duncan, D.	33	M	2 yrs	X	Sorbitrate, Nitroglycerine
C'Connors, C.	51	M	6 mos	X	Inderol, Nitroglycerine
Neal, R.	45	M	1 yr		Isordil Inderol Allopurinol Atromid
Shoberg, D.	56	M	1 yr		Hydrochlorothiazide, Quinadine
Tasca, A.	54	M	5 yrs	X	Nitroglycerine
Kee, M.	56	F	2 yrs		Nitro. Isordil, Quin. Atromid, Phenobarbital
Sullivan, W.	43	M	5 yrs		Inderol, Nitroglycerine
Ledbetter, E.	51	M	1 yr	X	Aldomet, Dyzide, Isordil, Inderol, Nitrospan
Bolton, L.	56	M	2 yrs		Isordil, Nitroglycerine
Emmons, D.*	45	M	6 mos	X	Nitroglycerine

*Dropped from study.

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STUDY OUTLINE

SCREENING EVALUATION	FIRST EXAM PERIOD							SECOND EXAM PERIOD										
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Alert form sent in	X																	
History & Physical	X																	
Exercise Treadmill & ECG	X						X	X										
Potassium-43 Scan *																		
1) at rest		X																
2) after exercise							X	X										
Laboratory (CBC, SMA-12, Urinalysis)																		
Frozen Plasma Sample																		
Frozen Urine Sample (>100 ml.)																		
Resting ECG																		
Evaluation Form																		

*Occasional studies were performed using Rubidium-81 when non-availability of Potassium-43 (production difficulties) would have interfered with this protocol sequence. Rubidium-81 is identical to potassium-43 for purposes of non-invasive myocardial imaging.

APPROVED

Table II

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PATIENT	EXERCISE PRE-PPHENILINE										
	HEART	DEFECT	RATIO	TIME	PULSE	BP	PVBP	HEART	DEFECT	RATIO	(MILS) TIME
DUNCAN	6.63	0.43	0.07	5-1/2	115	140/90	17500	8.51	1.96	.23	6
O'CONNORS	8.61	1.92	0.23	6-1/2	115	115/-	13525	9.33	4.95	.53	7
NEAL	6.81	1.55	0.23	7	155	122/92	18910	6.07	2.18	.35	9
SHOBERG	8.59	1.62	0.19	9	150	150/92	22500	9.14	3.85	.43	9
TASCA	7.92	0.91	0.13	9	150	150/80	22500	7.19	4.27	.60	9
KEE	5.60	0.85	0.15	8-1/2	167	160/80	26700	5.12	1.52	.30	7-1/2
SULLIVAN	6.22	1.47	0.22	8	130	110/70	14500	2.03	3.03	.39	3
LEDBETTER	9.15	7.57	0.18	5	136	180/110	25840	9.65	5.02	.52	6
BOLTON	7.02	.95	0.14	7	167	130/-	21710	7.44	5.14	.69	9

PATIENT	EXERCISE PRE-PLASERO										
	HEART	DEFECT	RATIO	TIME	PULSE	BP	PVBP	HEART	DEFECT	RATIO	(MILS) TIME
DUNCAN	6.83	0.43	0.07	6	125	120/80	15000	8.27	1.79	.22	7
O'CONNORS	8.61	1.92	0.23	5	120	120/80	14400	9.57	3.95	.42	6
NEAL	6.81	1.55	0.23	4	120	100/70	12000	6.66	2.65	.40	6-1/4
SHOBERG	8.59	1.62	.19	7	136	180/92	24480	8.14	2.71	.34	9
TASCA	7.92	0.91	.13	7-1/2	131	150/80	19650	6.84	3.94	.58	7-3/4
KEE 10 Jul To Control	5.60	0.85	.15	7	150	170/90	25500	5.82	2.22	.38	8
SULLIVAN	6.92	1.47	.22	8	125	120/-	15000	6.69	2.75	.92	9
LEDBETTER	9.15	1.57	.18	6	125	160/-	20000	9.49	5.20	.55	6-1/2
BOLTON	7.02	.95	.14	5	165	130/-	21450	6.52	3.70	.49	6-1/2

EXERCISE			EXERCISE POST PERIPHERAL						
HEART	DEFECT	RATIO	(MIN) TIME	(BPM) PULSE	(MMHG) BP	(MMHG) PKBP	(MIN) HEART	(MIN) DEFECT	(MIN) RATIO
9.01	1.94	.33	5	125	140/80	17500	10.15	2.13	.22
9.33	4.95	.53	7	125	140/80	21000	7.89	1.51	.20
6.07	2.13	.36	9	111	170/-	13320	6.67	2.73	.42
3.14	3.85	.43	9	125	155/60	19175	8.12	3.39	.42
7.13	4.27	.50	9	150	145/80	21750	7.28	4.44	.51
7.12	1.52	.30	7-1/2	150	150/80	22500	5.59	1.95	.34
7.13	2.03	.39	3	125	110/70	12000	6.75	2.00	.45
3.55	5.02	.52	6	131	180/-	23580	9.29	4.88	.53
7.44	3.14	.49	9	133	135/-	21300	6.55	3.52	.56

EXERCISE			EXERCISE POST PLACED						
HEART	DEFECT	RATIO	(MIN) TIME	(BPM) PULSE	(MMHG) BP	(MMHG) PKBP	(MIN) HEART	(MIN) DEFECT	(MIN) RATIO
8.27	1.79	.22	7	131	125/70	16375	8.97	1.75	.20
3.57	3.95	.42	6	111	114/70	12554	7.59	3.93	.52
			6-1/2	120	120/80	14400	4.89	4.07	.42
6.66	2.65	.40	6-1/4	125	130/80	18250	8.13	3.21	.40
			6	130	130/80	16900	6.13	2.52	.42
3.14	2.71	.34	9	131	180/90	23580	8.56	2.61	.31
6.84	3.94	.58	7-3/4	131	140/80	18340	6.95	4.03	.58
3.92	2.22	.33	8	167	175/90	29225	5.15	1.61	.31
			7	150	170/90	25500	4.50	1.64	.36
3.63	2.75	.92	9	125	125/-	15625	7.34	2.70	.37
3.49	5.20	.55	6-1/2	125	160/80	20000	9.55	4.06	.43
6.52	3.70	.49	6-1/2	155	130/-	20150	7.54	4.03	.62

TABLE III