Perhexiline Maleate in the Management of Patients with Angina Pectoris

A LONG-TERM ASSESSMENT

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SUMMARY

In a single-blind study lasting 6 months an entirely new anti-anginal preparation, perhexiline maleate (Pexid), was prescribed in a dose of 200 mg *b.d.* to 21 patients suffering from angina pectoris.

There was a statistically significant reduction in the average number of anginal attacks over the 6-month period in each subgroup studied. Half the cases studied were asymptomatic at the end of the period. Side-effects were reported in 16 patients; dizziness, headache, weakness, loss of weight and decreased libido being the commonest symptoms. No patient withdrew from the trial because of these symptoms, which disappeared within 4 weeks of continued therapy.

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Perhexiline maleate (Pexid) is an entirely new cardiovascular drug with the chemical formula:

2-(2,2 dicyclohexylethyl)-piperidine maleate.

It is not a beta-blocking agent and its actions in experimental work appear to be vasodilatation of the systemic and coronary arterial systems, with increased coronary blood flow; a reduction of left ventricular work; slowing of the exercise-induced tachycardia only; and a sustained bronchodilatation and diuretic effect.[1,2] The action of the drug is not fully understood but is not due to beta blockade or the inhibition of adenosine deaminase activity. It is unrelated chemically to any drug at present used in the management of angina pectoris.

Slowing of the exercise-induced heart rate by perhexiline is due to a direct action on the sino-atrial node. Animal studies indicate that this preparation has a quinidine-like action on the cardiac membrane and causes prolongation of both depolarisation and repolarisation times.[3]

The effects of the preparation on left ventricular function in man were recently determined and, using catheter techniques in patients with angina pectoris, to whom perhexiline had been orally administered for 2 weeks, it was found to cause a slight decrease in cardiac index without depressing left ventricular function. Both at rest and during tachycardia, there was improved oxygen extraction as well as improved lactate extraction.[4]

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Several clinical studies of the effects of perhexiline have been reported;[5-7] and this preparation was shown to considerably reduce the incidence of anginal symptoms.

Recent work also suggests that this preparation may have anti-arrhythmic effects in the human, particularly in relation to ventricular extrasystoles.[8]

Following an earlier assessment of a double-blind crossover trial with perhexiline maleate in the management of angina,[7] referred to in the text as Trial 1, a long-term continuous perhexiline maleate administration study was embarked upon. The main aim of this trial was to evaluate long-term effectiveness of perhexiline in angina pectoris, as well as to establish any side-effects or complications.

PATIENTS AND METHODS

Twenty-two patients with a history of angina pectoris of at least 6 months' duration were studied. There were 15 males (12 White, 2 Coloured and 1 Indian) and 7 females (5 White and 2 Coloured). One patient died after 4 months due to congestive cardiac failure and is not included in the analysis. Ages ranged from 46 to 78 years (Table I).

No patient had had a myocardial infarction in the 3 months preceding the study. No patient suffered severe hypertension, anaemia, hypothyroidism or any other apparent system disorder. All forms of treatment, apart from digoxin, diuretics and glyceryl trinitrate (when required), were discontinued for a period of 2 weeks before the commencement of the trial. The patients were given perhexiline 200 mg *b.d.* for the entire 6-month period of assessment. Twelve of the patients had taken part in the previous crossover trial and will be referred to as the group from Trial 1. The variables measured in the study included body weight, pulse rate, blood pressure, number of anginal attacks per week, nitroglycerin intake per week, resting and effort ECG, haemoglobin, white blood cell count, platelet count, prothrombin index, blood glucose, blood-urea, uric acid, alkaline phosphatase, urine analysis and serum glutamic oxalo-acetic transaminase (SGOT). These studies were performed each month, and at the same time the patients were given a 28-day diary to record their daily intake of nitroglycerin tablets and their daily number of anginal attacks. The patients were also given the exact number of perhexiline tablets to last for 28 days and had to report back and account for any unused tablets.

For statistical analysis as shown in Table I, 3 subgroups of the 21 patients were considered.

TABLE I. AGE OF PATIENTS STUDIED

	Patient group			
	Trial 1 (D-P)	Trial 1 (P-D)	New	Total
Sex				
Males	5	3	7	15
Females	0	4	2	6
Age — Mean	55,0 yrs	59,8* yrs	60,4 yrs	58,9* yrs
40 - 49	2	0	1	3
50 - 59	1	3	4	8
60 - 69	2	3	1	6
70 - 79	0	0	3	3

D-P (Patients from Trial 1 who were on perhexiline first and then placebo); P-D (Patients from Trial 1 who were on placebo first and then perhexiline).
* One patient's age was not certain.

Firstly there was the group of 5 patients from Trial 1 who had been on the perhexiline-placebo sequence in the earlier study (D-P). Secondly, there were 7 patients also from Trial 1 who had been on the placebo-perhexiline sequence (P-D), and finally 9 new patients who received perhexiline for the first time. The main reason for subdividing the patients was to distinguish any carry-over effect of perhexiline.

Fourteen patients were referred to an ophthalmologist for full ophthalmological examination including visual acuity, visual fields, lens examination and ocular tension studies, before and at the conclusion of the 6-month period.

RESULTS

Anginal Attacks

Before commencing the 6-month study the 9 new patients had had an average of 22,2 attacks, group D-P an average of 16,7, and group P-D 13 attacks of angina per week.

At the end of the 6 months the new patients were experiencing only 1,4 attacks of angina per week. (significance in reduction of attacks $P<0{,}001$ according to the paired *t*-test), D-P group 5,2 (significance $P<0{,}01$), and the P-D group 0,9 (significance $P<0{,}001$) attacks (Fig. 1).

No significant differences were observed between the months of treatment. As noted in the previous double-blind crossover study a decrease in the frequency of anginal symptoms occurred in the majority of cases and 11 of the 21 patients were totally asymptomatic. In 9 others the angina was of less severity and only one reported a deterioration of anginal symptoms. Angina decubitus was present in 6 of the present series and the number of their anginal attacks dropped from an average of 28 to an average of 3 attacks per week. There was an associated decrease in nitroglycerin intake and they were able to return to their normal daily activities.

Of the patients in the present study, 6 had previously been on beta-adrenergic blocking agents with an inadequate response. These agents included propranolol (300-400 mg daily) in 4 instances, practolol (400 mg *b.d.*) in 1, and oxprenolol (20 mg *t.d.s.*) in a further case. In all these patients improvement in anginal symptoms and reduction in nitroglycerin consumption were obtained within one month of treatment, and this effect was maintained during the 6 months of therapy.

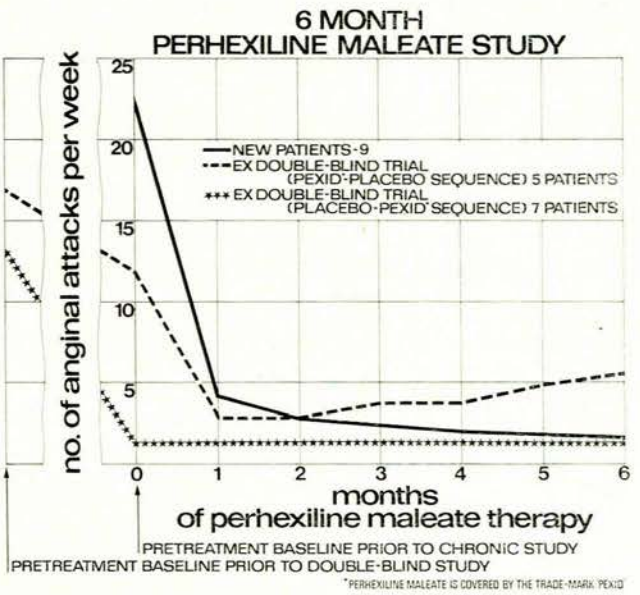

Fig. 1. Frequency of angina attacks during 6-month perhexiline maleate therapy.

Electrocardiogram Changes

At the initial visit ECG abnormalities were detected in 20 of the 21 patients. ST-segment depression after effort was recorded in 11 and frequent ventricular premature extrasystoles in 2 patients. At the end of the study there was less ST-segment depression on effort in 2 patients, and in a further 4 patients the inverted T waves at rest became upright. In the 2 patients with ventricular extrasystoles the arrhythmia disappeared in one and was reduced in the other.

Ophthalmological Assessment

In these 14 patients no ophthalmological differences were noted at the end of the period, with the exception of one, where posterior cortical changes of the lens in keeping with the patient's age were observed.

Side-Effects

Side-effects were similar to those previously reported, and no new side-effects were detected. Sixteen patients had one or more side-effects. In none were the side-effects of such intensity as to cause withdrawal from the trial.

Dizziness was most frequent and usually occurred within the first 7 - 10 days of therapy, passing off in all patients within 4 weeks. Less frequent side-effects were headache and weakness, which lasted for a few days. In 3 patients (out of a total of 5), where decreased libido had occurred, this improved towards the end of the study. In 1 of 3 patients with impotence, this may have been due to associated diabetes. Other rare side-effects of a transient nature included arthralgia, frequency of micturition and constipation (Table II).

TABLE II. SIDE-EFFECTS ENCOUNTERED IN 21 PATIENTS

Symptom	No.	%
Dizziness	11	52
Weight loss (>2 kg)	11	52
Decreased libido	5	24
Headache	4	19
Weakness	4	19
Impotence	3	14
Frequency	2	10
Constipation	2	10
Arthralgia	1	5
No symptoms	5	24

During the 6-month study there was a mean loss of weight of 2,9 kg. Six patients lost less than 5 kg, 5 patients lost between 5 and 10 kg, and 1 exceptional patient with marked oedema lost 17,7 kg. Approximately two-thirds of this loss occurred within the first 2 months. However, a weight gain ranging from 0,5 to 3,2 kg occurred in 7 patients. In 2 patients weight remained unchanged.

Laboratory Investigations

On 4 separate occasions, including an initial base line assessment, haematological evaluations were performed and no abnormal effects on haemoglobin concentration, platelet count, white cell count and differential count were noted.

The prothrombin index remained unchanged, with the exception of one case where it dropped to 86%. No abnormal change was detected in blood-urea, uric acid, alkaline phosphatase and blood glucose levels. Urine analysis showed no abnormalities.

In 15 patients the SGOT levels remained within normal limits. However, in 4 patients values rose to between 20 and 40 units (normal less than 20 units), and in 2 the maximum values reached 120 and 90 units respectively.

Subsequent to this trial, full liver function tests, including albumin-globulin ratios, protein electrophoresis, bilirubin, alkaline phosphatase, creatinine phosphokinase and lactic dehydrogenase estimations, as well as liver biopsies, were all normal and the impression was that the raised SGOT levels settled in most patients and dropped considerably in the others.

CONCLUSION

Statistically significant reductions in the average number of anginal attacks were recorded over the 6-month period in all three subgroups studied, half the cases being totally asymptomatic at the end of the period.

No new side-effects were detected, and the same side-effects previously recorded[7] were encountered again. In only one patient of the group studied were the anginal attacks not reduced. In no patient was the trial discontinued because of side-effects or intolerance to the drug.

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