Effects of Sustained Isometric Handgrip on Ventricular Systolic Time Intervals in Patients with Ischemic Heart Disease

Inotropic State of the Left Ventricle during Treatment with Perhexiline Maleate and with Propranolol

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SUMMARY

It was found from our previous studies that patients suffering from ischemic heart disease with angina, showed either one of the patterns of the left ventricular systolic time intervals on isometric handgrip exercise.

Patients in class I or II NYHA showed a shortened pre-ejection period corrected for heart rate (PEPI), and a prolonged ejection period corrected for heart rate (LVETI) together with a decrease of the PEP/LVET ratio. This response is normal, because it has also been found in normal subjects.

The patients in class III or IV NYHA showed a prolongation of PEPI, shortening of LVETI and an increase of the PEP/LVET ratio. This response is abnormal, because it occurs in patients with impaired cardiac performance and in ischemic ones with widespread asynergic areas.

Our aim here is to study the response of these 2 groups of patients treated for a 4-week period with perhexiline maleate. This new drug is chiefly used as anti-anginal drug, though it also has anti-arrhythmic properties.

The results show that the response of the left ventricle to isometric handgrip exercise in class I or II patients following perhexiline maleate treatment, is almost normal, thus confirming that the drug has no side effects on the cardiodynamics checked by the left ventricular systolic time intervals.

The responses of class III or IV patients after perhexiline maleate become normal. This shows that the drug acts by removing the contractile dysfunction. It can reasonably be assumed that this takes place following the elimination of the ischemia induced dyssynergic areas.

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The effect of this drug has also been evaluated from a clinical point of view. A marked decrease in the frequency of anginal crises and the consequential reduction in the consumption of trinitroglycerin pills during perhexiline maleate treatment could thus be observed.

Additional Indexing Words:

Angina Triple product Polygraphic tracing Isometric exercise
Left ventricular function Beta-blocking agent

MYOCARDIAL ischemia causes asynergic areas in the ventricular wall responsible for the various degrees of impaired contractility.^{6),23),26),34)}

Any physical stress, such as the isometric handgrip exercise, can produce or enhance impaired contractility.^{5),21),29),32),48),49)}

Signs of left ventricular failure are the following: A) increase of end-diastolic pressure, B) decrease of dp/dt , C) decrease of V_{max} , D) decrease of the ejection fraction as well as lengthening of the pre-ejection time (LVET), and E) increase of the ratio of the 2 systolic times (PEP/LVET).^{4),15),18),20),22),25),35),36),41),55)}

In previous studies,⁵⁰⁾ we have demonstrated how different patients suffering from ischemic heart disease with angina, show 2 behavior patterns of left ventricular systolic time intervals after handgrip exercise.

Some of them, classified as Ist and IInd class NYHA patients, show a shortening of the pre-ejection period corrected with heart rate (PEPI) and a decrease of the PEP/LVET ratio. These are the reactions which can be observed in normal subjects and may be considered as hemodynamic responses to this exercise.^{33),45)}

Other patients, belonging to the IIIrd and IVth class NYHA show a lengthening of the PEPI, a shortening of the LVET and increase of the PEP/LVET ratio. We have already seen this behavior in impaired contractility of the left ventricle.^{2),16),46)}

The purpose of this paper is to establish whether the 4-week treatment with perhexiline maleate modifies the response in those patients suffering from ischemic heart disease with angina, who respond to the handgrip exercise with either type of behavior in the left ventricular systolic time intervals.

Perhexiline maleate is a new drug which is essentially an antianginal agent.^{8)-11),31),37),43)} It also has, however, antiarrhythmic properties.^{13),53),54)} The mechanism of action has not yet been established. However, although it is not a cardioselective beta-blocking agent, it has a similar favorable effect.

METHOD

We studied 20 patients with ischemic heart disease (14 males and 6 females, ages ranging from 46 to 82). During the experiment it became necessary to discard 3 subjects. In 2 of them perhexiline maleate caused dizziness. The other one, who had already been suffering from repeated attacks of angina, died 6 days after taking the drug, with acute myocardial infarction. However, we do not believe that any responsibility for this can be attributed to the use of the drug. Therefore, our results were based on 17 patients.

Before starting the experiment the patients were submitted to a 1-week wash-out period, during which only trinitroglycerin (TNG) was permitted for the treatment of anginal attacks. After this period a polygraphic tracing was recorded on patients both at rest and at conclusion of a 3 min period of isometric handgrip exercise, performed at tension levels of 30% and 50% of the maximum voluntary contraction. Each patient was instructed to avoid a Valsalva maneuver during the handgrip exercise. In some cases it was not possible to obtain 50% of the maximal contraction owing to the onset of either angina or muscular exhaustion. PEPI and LVETI and the PEP/LVET ratio⁽⁵⁶⁾⁻⁽⁵⁸⁾ were calculated from the recorded polygraphic tracing. These calculations were derived from measurements of 5 consecutive cardiac cycles and the average of the data obtained was then considered. In this way it was possible to determine the behavior curve relative to the handgrip exercise of each patient. By multiplying the heart rate by the arterial systolic pressure and the total ejection time (so called triple product), we obtained indications concerning the myocardial oxygen consumption behavior.
(14), (17), (28), (51)

Every day each patient was given 300–400 mg doses of perhexiline maleate or 120 mg of propranolol. A cross-over comparison amongst patients was made as an experimental test. The period of drug treatment for each patient was 4 weeks, and the patients for each drug were selected at random. A 2-week wash-out period with placebo was interpolated between the 2 active treatments. Conditions of “single blindness” were maintained between placebo and perhexiline since the tablets were undistinguishable in form from the original ones. Conditions of “single blindness” did not hold for propranolol since the obvious effects of bradycardia could easily be detected even by the patient himself.

The polygraphic tracing during handgrip exercise was recorded at the end of the 4-week period of treatment with the 1st drug, at the end of the following 2-week period of wash-out with placebo and again at the end of the 4-week period of treatment with the 2nd drug. Thus the data of PEPI, LVET, and the PEP/LVET ratio were obtained during 30% and 50% handgrip exercise at the end of the various periods of treatment. As far as the polygraphic tracing data were concerned, a cross-over analysis of variance was performed only for the changes relative to the 30% handgrip exercise, since complete data with balanced sequences were available only for this parameter. With this test we noticed that the changes in the polygraphic data were not affected by the period effect. Consequently, the following tests on the 50% exercise with patients subdivided into groups according to NYHA criteria, were performed by a paired student's t-test, with comparison of active drugs versus base placebo.

A cross-over variance test was performed in order to have a statistical evaluation of the number of angina crises and the patient's consumption of TNG pills. We used the differences' method reported by Li.³⁰⁾ The variable considered was the number of attacks and pills in the last 2 weeks of active treatment as reported by Armstrong et al.¹⁾ This was in order to avoid the influence of carry over effects and to choose a period in which perhexiline maleate consumption could reach a constant drug metabolic condition of equilibrium.

It must be pointed out that the data concerning the attacks and the pill consumption were submitted to metemetric transformation ($x' = x + 0.5$) in order to stabilize the variance.

RESULTS

The data relative to the triple product, that is, the heart rate multiplied by arterial systolic pressure and total ventricular ejection time are summarized in Fig. 1. It can be seen how the triple product increases with the degree of handgrip exercise. The rise of the value is only slight in moments of stress at the end of the period of treatment with propranolol, but on the average it becomes less noticeable at the end of the period of treatment with perhexiline maleate.

However, because of the high degree of individual variability and the limited number of cases tested, the cross-over variance concerning the data of the triple product changes after a 30% handgrip exercise, did not show a significant difference between perhexiline maleate and propranolol.

The same analysis excludes the possible period effect on the drug's action.

Since we did not have enough patients to submit to 50% isometric stress, we could only perform a paired student's t-test for data between perhexiline maleate and propranolol. Even here the rise of the triple product under stress was, on average, lower with perhexiline although it was still not significant.

The behavior of PEPI in Ist and IIInd class and IIIrd and IVth class NYHA patients is shown in Fig. 2 respectively as groups a and b. It can be seen from group a that PEPI decreased during stress provoked by the isometric handgrip exercise when patients were treated both with placebo and perhexiline maleate as well as with propranolol. From group b it can be seen that during isometric exercise PEPI increased when the patients were treated with placebo and propranolol, while it decreased with perhexiline maleate.

Statistics show that the changes during perhexiline maleate treatment are highly significant ($p < 0.01$) compared with the placebo treatment. Between the latter and propranolol there is a lower level of significance ($p < 0.1$).

In the cross-over variance based on the data taken from all the patients, with regard to the changes of PEPI after a 30% stress, the difference between

Fig. 1. Behavior of triple product in all patients checked. On the ordinate, run the percentage variations concerning the base values, and on the abscissa, the levels of isometric exercise.

Fig. 2. Behavior of PEPI in ischemic patients. Above the percentage variations in reference to base values for each level of the handgrip exercise. Below the average values found in patients with the standard deviations and relationship between drugs and placebo. Group a: I and II NYHA class patients; Group b: III and IV NYHA class patients.

perhexiline maleate and propranolol is statistically significant. In fact, while perhexiline maleate under stress gives an average decrease of 7.06 msec, propranolol gives a PEPI increase of 5.93 msec.

The behavior of LVETI is shown in Fig. 3. It can be seen from group a that in Ist and IInd class NYHA patients there is a relationship between LVETI and the degree of stress. This increase could be noticed even when the patients were treated with perhexiline maleate and propranolol.

The statistics do not give evidence of any significant change between the 2 drugs on one side and the placebo on the other.

It can be seen from group b that in IIIrd and IVth class NYHA patients, LVET undergoes some changes. The handgrip exercise, after placebo treatment, gives a decrease of this index. When the same exercise follows a perhexiline or propranolol treatment an increase of LVETI can be observed.

The changes caused by the drugs compared to those caused by the placebo are highly significant both during 30% and 50% stress ($p < 0.02$). The cross-over variance carried out on data concerning the changes under

Fig. 3. Behavior of VLETI in isochemic patients. Above percentage variations in reference to base values for each level of the handgrip exercise. Below the averages of the values found in the patients with standard deviations and relationship between drugs and placebo. Group a: I and II NYHA class patients; Group b: III and IV NYHA class patients.

30% stress did not show any significant difference between the 2 active drugs on the LVETI.

The behavior of the ratio PEP/LVET during handgrip exercise carried out by ischemic patients is shown in Fig. 4. In group a the curve refers to Ist and IIcd class patients. During stress the index, both in patients treated with placebo and in those treated with perhexiline maleate and propranolol becomes smaller. There is no significant change in the behavior between the 2 drugs and the placebo.

In group b the ratio PEP/LVET refers to IIIrd and IVth class patients. It is clear how handgrip exercise following placebo increases this ratio, whereas it causes it to decrease after perhexiline maleate treatment.

The changes caused by perhexiline maleate compared to those caused by the placebo are statistically significant both with 30% ($p < 0.01$) and 50% ($p < 0.05$) stress. Whether the patients were treated with propranolol or with placebo the results were the same, but statistically there is a slight difference ($p < 0.05$ with 30% and 50%).

Fig. 4. Behavior of the PEP/LVET ratio in ischemic patients. Above percentage variations in reference to base values for each level of the handgrip exercise. Below the averages of the values found in each patient with standard deviations and relationship between drugs and placebo. Group a: I and II NYHA class patients; Group b: III and IV NYHA class patients.

Fig. 5. Number of angina crises compared to placebo.

Fig. 6. Intake of TNG pills compared to placebo.

The variability analysis was carried out in the same way for PEPi and LVETi. It showed a statistically significant difference for the PEP/LVET ratio, between perhexiline maleate (average ratio variability=0.03) and propranolol (average ratio variability=0.01).

In Figs. 5 and 6 the clinical effects of perhexiline maleate and propranolol are shown in relation to the number of angina crises (Fig. 5) and TNG pills taken by the patients (Fig. 6). Both active drugs decrease the number of angina crises and TNG consumption by 65–75% compared to the values obtained with placebo.

The variability analysis performed in accordance with a cross-over did not show significant differences with regard to the frequency of attacks and pill consumption in the second 2 weeks between the 2 active treatments.

However, as can be seen from the figures, we had a marked clinical improvement with propranolol, 3–4 days following treatment, but it disappears just as markedly when the drug is withdrawn.

With perhexiline maleate the 65–75% decrease of angina crises and TNG pill intake is obtained on the other hand only after 6–10 days, and the effects wear off just as slowly when the drug is withdrawn.

DISCUSSION

The results lead us to make some interesting findings. First of all the increase of the triple product during handgrip exercise is established.^{14),28,,48)} This is indicative of higher myocardial oxygen consumption.²³⁾ It has been demonstrated that the handgrip exercise can emphasize the degree of failure of left ventricular performance in patients with different types of cardiopathy.^{18),19)} This happens particularly in those with ischemic heart diseases when neither the ST segment displacement, nor angina symptoms^{18),29)} are taken as evaluation criteria of the stress response, but rather as indices of myocardial contractility.^{2),20),38),52)} In patients performing a stress at the end of perhexiline treatment, the oxygen consumption increase is lower than in those observed both after placebo and after propranolol. Although from a statistical point of view these data need to be verified on a larger number of patients, they appear to be worthy of note.

This behavior during treatment with perhexiline maleate is similar to that observed with other antianginal drugs which act through a metabolic type action. It has not yet been demonstrated whether this effect is obtained directly with the perhexiline maleate just as would be with any beta-blocking drug, or indirectly by the peripheral effects which it seems to produce. The latter supposition seems to be the most probable one,^{24),39),44)} and for this reason,

today perhexiline maleate is considered an anti-anginal drug which has the same effects as a beta-blocking agent although it is not included in this category.^{10), 31), 43)}

As far as the behavior of the left ventricular systolic time intervals is concerned, the 2 types of results depending upon grade of the ischemic disease, were confirmed.⁵⁰⁾ In the Ist and IIInd class patients the handgrip exercise produces: decrease of PEPI, increase of LVETI and decrease of the ratio PEP/LVET. This response is normal since it is also observed in patients with no cardiovascular disorders. The responses to handgrip exercise in the same patient after perhexiline maleate and propranolol intake are not different from the normal responses mentioned above. This proves that perhexiline maleate has no negative effect on the cardiodynamics of those patients checked by means of the left ventricular systolic time intervals, at least when they are treated with the doses used during the observation period.

In the IIIrd and IVth class patients, isometric stress leads to a lengthening of PEPI, a shortening of LVETI and an increase of the ratio PEP/LVET. This response is abnormal. It can in fact be observed in patients with heart failure^{3), 40)} and in ischemic cardiopathy with wide asynergic areas.^{6), 7), 12), 27)} Responses to handgrip exercise carried out on the same patients after perhexiline maleate are normal. This consequently proves that perhexiline maleate acts by removing the contractile cardiac dysfunction and this probably takes place because of the elimination of asynergic areas caused by ischemia.

In studying the effects of perhexiline maleate on the number of angina crises and TNG pill consumption, we confirmed its properties as an anti-anginal drug, and from the conclusions we reached we have the impression that it acts through a cardiovascular mechanism.

In conclusion, it seems likely that perhexiline maleate decreases myocardial oxygen consumption. It normalizes the left ventricular systolic time intervals when they are abnormal, but does not change them when they are normal. Finally it decreases the number of angina crises and TNG pill consumption.

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