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Penbutolol and Molsidomine Synergism in Angina Pectoris. A Double Blind Ergometric Trial

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Summary. In order to test the additional efficacy of the combination of a beta blocker (penbutolol 40 mg single dose) with molsidomine (2 mg single dose), a double blind cross-over trial was performed in 30 patients with stable angina pectoris. Stress tests were done before and 1 h after the beta blocker alone and the combination therapy. Some training effect could be detected on comparing results from the first and second days. Combined therapy showed a better response of resting systolic arterial pressure, resting and maximal diastolic pressure, heart rate gain (from rest to maximal effort) and particularly in the angina severity score. All of these variables changed significantly in comparison to the beta blocker alone, 46 out of 60 post-drug ergometric studies were negative; of the 14 positive tests, 11 followed the beta blocker and only 3 the combined therapy. The combination of a preload reducer molsidomine and a beta blocker may be adequate for patients only partially compensated or with cardiomegaly and/or a depressed ejection fraction.

Key words: Molsidomine, penbutolol, angina pectoris; angina severity scores, ergometric tests, beta-blocking agents, pre-load reduction

The search for efficient pharmacological treatments for patients with stable angina is based on the initial trials of Russek [1] and Aronow [2, 3]. Summation of beneficial effects appears to depend on selection of drugs with different mechanisms of action on myocardial oxygen consumption.

The use of beta blockers in the prophylactic therapy of angina pectoris [4, 5] and for prevention of reinfarction [6] is based on their bradycardiac and negative inotropic properties. However, their use is restricted by the occurrence of signs of left ventricular failure when the dose is increased [7]. Therefore, it appears useful to combine them with vasodilator drugs, which reduce cardiac preload and counterbalance some of the untoward effects.

In this connection, it appeared of interest to compare the additive effects of a delayed-action vasodilator (molsidomine) to those produced by the non-cardioselective beta-blocking agent, penbutolol.

Material and Methods

Thirty coronary patients participated in the study, 28 men and 2 women, whose ages ranged between 47 and 83 years. All patients clinically had stable angina pectoris and clear evidence of ischaemia in a selection test on a treadmill. In the latter they all showed angina and depression of the ST segment greater than 1.5 mm (at 80 m.s. from point J) on maximal effort. All of them had performed 2 or more exercise tests before selection and so were familiar with the technique.

Fourteen patients had previously had an infarct (anterior in 4 and diaphragmatic in 10); 20 of them were hypertensives.

The study design was of the double-blind, cross-over type. Patients were adequately randomized in two therapy sequences: one group of 16 patients received penbutolol + placebo (P) at first, followed by penbutolol + molsidomine (P + M); the other group of 14 patients received the drugs in the inverse sequence. A one-week wash-out period was allowed between the two therapeutic phases.

The study was carried out on single days and comprised 1 basal stress test (without drug treatment) and a further test 1 h after oral intake of the

Table 1. Mean changes during the P–P+M treatment sequence

Parameter	Basal values		Post-drug values	
	1st day	2nd day	1st day P	2nd day P+M
Resting heart rate (HR, beats/min)	71.4	68.6	62.8	63.9
Resting syst. art. pr. (SAP, mmHg)	149	140.0	131	108
Exercise time (min)	7.3	9.8	11.1	14.3
Max. ST depression (mm)	2.4	1.8	1.1	0.4
Max ST/exercise time (ratio) (mm/min)	0.5	0.3	0.2	0.0
ST depression at equal load (mm)	2.3	1.7	0.5	0.2
ST depression after 5′ recovery (mm)	2.2	1.8	0.9	0.4
Angina score (0–4)	2.6	2.4	1.4	0.7
Max HR (beats/min)	121	115	103	99.2
HR gain (beats/min)	45.5	44.9	40.7	35.3
HR at equal load (beats/min)	114	106	89.3	87.9
HR after 5 min recovery (beats/min)*	45.4	40.4	36.9	31.0
Max SAP (mmHg)	187	176	162	146
Max diastolic art. pr. (mmHg)	105	99.1	97.2	88.4
Max double product (HR × SAP/100)	226	200	169	147
Double product at equal load (HR × SAP/100)	225	204	142	126

* HR descent from peak value to 5 min recovery

Table 2. Mean changes during the P+M–P sequence

Parameter	Basal values		Post-drug values	
	1st day	2nd day	1st day P+M	2nd day P
Resting heart rate HR (beats/min)	75.9	70.5	72.3	70.1
Resting syst. art. pr. (SAP, mmHg)	151	140	115	131
Exercise time (min)	10.4	10.9	15.1	13.5
Max ST depression (mm)	1.9	1.9	0.0	0.5
Max ST/exercise time (ratio) (mm/min)	0.2	0.2	0.0	0.0
ST depression at equal load (mm)	1.9	1.9	0.0	0.1
ST depression after 5′ recovery (mm)	1.8	1.9	0.0	0.4
Angina score (0–4)	2.6	2.5	0.3	1.1
Max HR (beats/min)	121	110	104	100
HR gain (beats/min)	46.1	39.6	31.9	36.7
HR at equal load (beats/min)	112	104	90.4	88.3
HR after 5′ recovery (beats/min)	40.0	34.0	30.8	32.0
Max SAP (mmHg)	180	179	154	162
Max diastolic art. pressure (mmHg)	109	105	94.3	98.9
Max double product (Max DP = HR × SAP/100)	233	201	160	164
DP at equal load (HR × SAP/100)	226	197	137	137

appropriate treatment (post-drug). Thus, a total of 4 stress tests per patient were performed; the dose of penbutolol sulphate was 40 mg, and that of molsidomine was 2 mg.

Ergometric tests were maximal, multi-stage, symptom-limited tests (angina, frank dyspnoea or fatigue) using a modified Balke protocol. The parameters evaluated in each ergometric test are shown in the tables. No tests lacked data and no data were lost, so 120 ergometric studies (basal and 60′ post-drug) were performed.

Statistical analysis was carried out using Grizzle's model [8] for two-period clinical studies with cross-over sequences, according to the outlines proposed by Hill, Armitage and Davies [9].

All but three variables can be considered of the quantitative type, thus allowing use of parametric ANOVA. It seems reasonable to treat angina scoring, although of ordinal type, as quantitative, as regards differences between post-drug and basal values. Times until 1 or 2 mm depression of the ST segment cannot be considered quantitative, since many post-drug tracings did not show any depression.

SAS software was used for data analysis. The significance level adopted for all tests was 5%.

Results

A. Basal Data

In the initial tests (without drug) the basal values for all variables were recorded on the first study day and again on the second day after a one-week wash-out period. Effects of the "period" (1st day vs. 2nd day, probable training effect) and the "residual" effects of

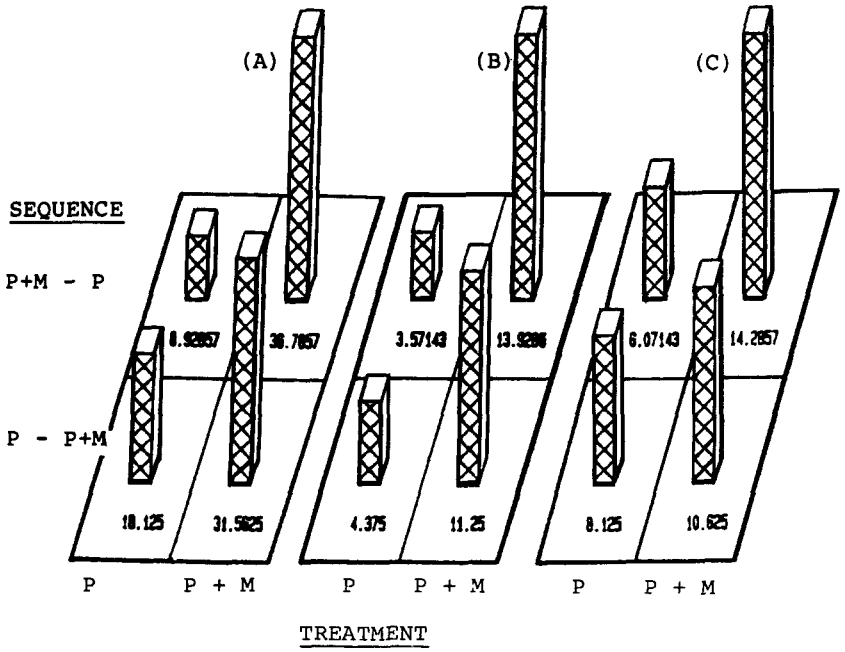

Fig. 1 A Resting systolic arterial pressure; **B** resting diastolic arterial pressure and **C** maximal diastolic arterial pressure. Mean negative changes in each variable respect to the basal value (without drug).

medication were analyzed by means of Student's test for paired and unpaired samples.

The mean basal and post-drug values and their differences are shown in Tables 1 and 2.

In general, tests carried out on the second day showed a better performance than those on the first day, which was regarded as a training effect and/or familiarization with the technique; for example, basal heart rate was lower on the second day in both sequences (1st day 71.4 and 75.9; 2nd day 68.6 and 70.6 beats/min). The maximal double product also showed similar behaviour, being lower on the second day of study for both sequences (1st day 266.4 and 233.3; 2nd day 199.9 and 201.3). No residual effect could be found, so the statistical tests to determine the treatment effects are valid.

B. Post-Drug Data

B.1. P–P+M Sequence. Data of interest. The HR at rest decreased more after P than after the fixed combination of P 40 mg + M 2 mg (−8.7 and −4.7 beat/min with respect to basal values). However, the SAP at rest was lower with P+M than with the beta blocker alone (−18.1 and −31.6 mmHg). The same behaviour was observed for maximal systolic and diastolic pressures. The severity of effort-induced angina was reduced by both treatments, but particularly by the combination.

B.2. P+M–P Sequence. In this sequence, there was a smaller difference between the 1st and 2nd days, with more homogeneous behaviour of exercise time (10.4 and 10.9 min, respectively) and of electrocar-

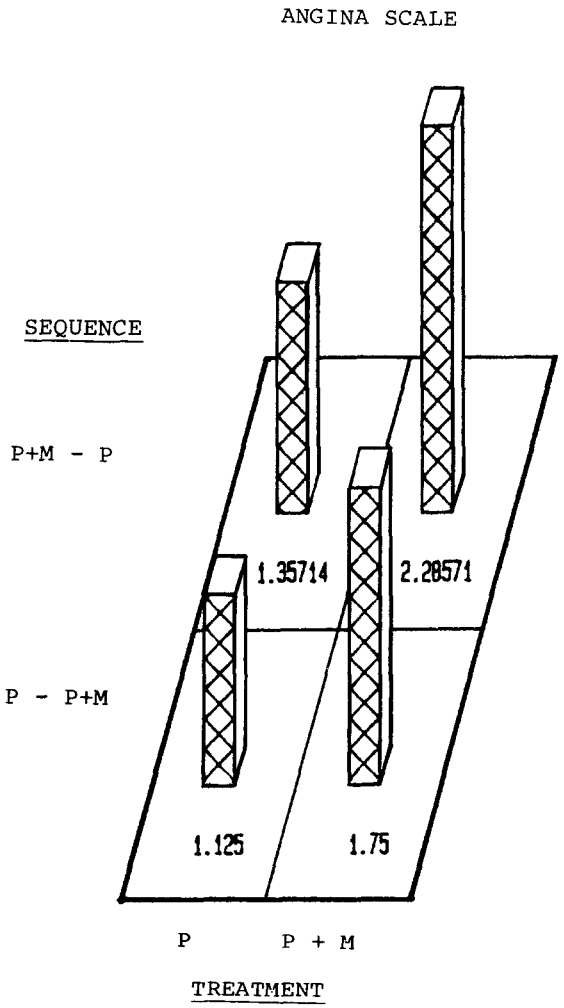

Fig. 2. Mean reduction in angina score (0–4 point scale) from the basal values (without drug)

diographic (1.9 mm in both basal tests) and clinical ischaemia.

As in the P–P + M sequence, more relative bradycardia was found after penbutolol than after the P + M association, and there was a greater hypotensive effect (at rest and effort) of the latter than after the beta blocker alone. Exercise time was longer with P + M than with penbutolol (4.7 and 2.6 min difference from basal values). Also, angina was less severe with the combination than with the beta blocker alone.

B.3. Overall Analysis. The basal HR was lower, although not significantly so, after penbutolol than after the combination. With respect to other variables, the mean responses during the combination were as marked as after penbutolol alone. Larger changes were found for P + M in 5 variables: systolic arterial pressure at rest, diastolic arterial pressure at rest and effort, HR gain and, particularly, the degree of severity of angina (Figs. 1, 2). Of the 60 post-drug ergometric studies, 46 were stopped due physical exhaustion without occurrence of clinical or electrocardiographic signs of ischaemia. In 6 post-penbutolol and 2 post-combination instances, ergometric testing was interrupted due to angina plus ST depression. Three tests were stopped due to isolated angina, all in subjects receiving penbutolol, and 3 due to ST depression – in 2 on penbutolol and 1 on the combination. In all, there were 14 positive post-drug ergometric tests, 11 of them after the beta blocker.

The number of patients that failed to reach 1 and 2 mm depression of the ST segment during the course of the post-drug ergometric test was greater for the association than for penbutolol alone. Only 4 of 30 patients reached a 1 mm depression after P + M, compared to 11 after Penbutolol. Only 1 of the 23 subjects who had previously had a 2 mm depression showed this effect after the combination, compared to 5 after the beta blocker.

Discussion

This study raised certain methodological problems that called for careful statistical treatment; before analyzing the effects of the drugs, the existence of a training or habituation effect on the 2nd day of study with respect to the 1st day, had to be taken into account. Indeed, the statistical study showed lower HR, SAP and DP in the basal ergometric test on the 2nd study day. Another problem to be considered is the probable effect of the first day medication on the tests performed one week later.

Neither penbutolol (halflife 27 h; [10]) nor molsidomine (half-life 2 h) given in single, isolated doses appear likely to be of any importance in this respect. Statistical analysis also ruled out this possibility. Due to the training effect, treatment analysis was first carried out separately for each sequence and then globally.

The P + M association was statistically superior to administration of the blocker alone as regards the systolic and diastolic arterial pressures at rest and effort diastolic pressure, thus demonstrating a greater hypotensive effect; the pulse increase from rest to maximal effort was also higher with the combination. It is important to note the action of P + M on the degree of severity of the exercise-induced ischaemia.

Of the 60 post-drug ergometric studies, 46 (76.6%) were negative as regards ST depression and/or angina; of the remaining 14 that were positive during treatment, 11 were positive with the beta blocker and only 3 (5%) with the combination.

In a study by Witchitz et al. [11], the effects of beta blockers alone were compared with those induced by their combination with isosorbide dinitrate, nifedipine and molsidomine; it was concluded that these combinations improved the results obtained with the beta blocker [11].

Drug combinations of this type have been reported since shortly after beta-blocking agents first came into clinical use. Russek, in 1968 [2] and Battock et al. [3] and Aronow and Kaplan [4] in 1969 studied the possible synergism of propranolol + isosorbide dinitrate, but with barely conclusive results.

In spite of the fact that beta blockers are widely accepted for the treatment of angina pectoris, they occasionally fail fully to control angina, and then they require combination with another drug. On the other hand, beta blockers sometimes produce ventricular failure, as shown by a fall in cardiac index and in ejection fraction, which can be balanced by a vasodilator agent.

In another study [5], left ventricular function, determined by radioisotopic angiography, improved after the administration of vasodilators as regards the ejection fraction and regional wall motility; beta blockers then produced a non-significant fall in those parameters.

Molsidomine, a delayed-effect venodilator agent, reduces venous return and the size of the left ventricle [16]. Its activity as an antianginal drug when used alone has been the object of several reports [17–19]. The present findings appear to indicate that molsidomine associated with beta blockers may constitute an adequate therapy for patients partially compensated with beta blockers alone, or those with cardiomegaly and/or a depressed ejection fraction.

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