

Combination of Metoprolol with Molsidomine in the Treatment of Angina Pectoris

J. P. van Mantgem, K. I. Lie, and A. W. Matroos

Wilhelmina Gasthuis, Department of Cardiology, Amsterdam, The Netherlands

Summary. In a randomized controlled trial 31 patients, who were unsuccessfully being treated with metoprolol for severe angina pectoris, were also given molsidomine or placebo. During an exercise test, there was no difference between the groups in heart rate or blood pressure. There was a tendency towards a mild, significant improvement in exercise performance in the molsidomine-treated group, in whom both workload and exercise duration increased after two weeks of treatment. In the placebo-treated group, these parameters decreased.

Key words: angina pectoris, metoprolol, molsidomine; combination therapy, exercise test

Beta-adrenoceptor blocking agents are the accepted therapeutic agents for chronic, stable, exertional angina pectoris. A number of patients are either unable to tolerate the required dosage or do not respond adequately, thus necessitating additional therapy. Long acting nitrates are conventionally added and more recently calcium channel blockers have been advocated in such patients (Lynch et al. 1980; Leon et al. 1981; Tweddel et al. 1981; Subramanian et al. 1982; Daly et al. 1982; Bassan et al. 1982). However, in some patients these compounds are also associated with troublesome side effects, such as headache, cardiac failure and AV conduction disturbances (Deanfield et al. 1983; Opie and White 1980; Robson and Vishwanath 1982).

Molsidomine (*N*-ethoxycarbonyl-3-morpholino sydnonime), a member of the sydnonimines, has powerful vasodilator properties, like the nitrates, but it appears to have a longer duration of action due to lack of first pass metabolism (Majid et al. 1980; Balakumaran et al. 1983). In this preliminary study the acute efficacy and interaction of the combination of molsidomine with metoprolol in patients with chronic severe angina pectoris has been evaluated.

Materials and Methods

Thirty one hospitalized patients (18 males and 13 females; age range 45 to 75 years) with a history of chronic, stable, exertional angina pectoris for at least

3 months agreed to participate in the study. The patients had at least 5 anginal attacks per week, and none had responded adequately to beta blocker therapy alone or in combination with long acting nitrates. They all had exercise-induced ST segment depression and evidence of confirmed artery disease on coronary arteriography (> 70% luminal narrowing), or documented recent transmural myocardial infarction. The patients were hospitalized because of their severe anginal condition; the majority was awaiting surgery. The hospitalization permitted close observation of the effects of the combination.

Women of child bearing age and patients with severe hypertension, cardiac failure, higher degrees of AV block, other systemic diseases and with any need for additional cardiovascular treatments were excluded.

The trial, which lasted for 4 weeks, followed a randomized, parallel double blind design. The patients received metoprolol 100 mg b.d. in combination either with placebo or molsidomine 2 mg b.d. During the study period no other cardioactive medication was permitted, except sublingual glyceryl trinitrate to control exertional angina.

A daily record was kept of the anginal attacks and of the numbers, of glyceryl trinitrate tablets consumed. The baseline assessment included history, physical examination chest X-ray, laboratory tests and a symptom-limited maximal bicycle exercise test. Physical examination was repeated at weekly intervals and the other investigations were done fortnightly. On termination of the study, the patients and the physicians noted their impression of improvement.

Significance testing for the effect of treatment on the frequency of anginal attacks, nitroglycerine consumption, exercise duration and workload achieved employed the Mann-Whitney U test (Siegel 1956) applied to the difference between the two groups between weeks 0 and 2.

Results

Thirty one patients entered the study; 2 patients, 1 in each group, were withdrawn due to uncontrollable angina, and 1 due to a skin rash not related to mol-

sidomine therapy. In no instance was treatment terminated because of adverse effects. Thus, 28 patients completed the study, 14 each in the molsidomine and placebo groups. There were 8 males and 6 females in each group, their mean ages were 63 and 62 years, respectively, and the groups were compa-

Table 1. Mean (\pm SD) heart rate and systolic and diastolic blood pressures during exercise

Treatment:	P*	M**	P*	M**	P*	M**
	Heart rate [beats/min]		Systolic BP*** [mmHg]		Diastolic BP*** [mmHg]	
<i>At rest:</i>						
<i>Before treatment:</i>						
mean	65.2	63.8	137.7	138.3	80.4	78.8
\pm SD	12.1	9.1	17.8	17.8	11.8	10.0
<i>During hospitalization:</i>						
mean	60.6	56.0	135.0	124.2	77.1	78.1
\pm SD	13.3	6.7	17.0	20.4	10.3	9.9
<i>At maximal workload:</i>						
<i>Before treatment:</i>						
mean	109.3	97.1	166.9	153.3	83.5	81.7
\pm SD	14.1	15.1	28.1	23.0	11.3	10.3
<i>During hospitalization:</i>						
mean	99.0	94.2	160.0	156.9	78.5	84.2
\pm SD	21.6	11.5	26.8	23.9	12.3	12.7
<i>After 6 min recovery:</i>						
<i>Before treatment:</i>						
mean	79.1	70.5	142.3	140.5	79.2	77.0
\pm SD	16.1	11.9	26.6	14.0	14.7	8.9
<i>During hospitalization:</i>						
mean	69.1	64.0	136.1	136.5	76.4	80.0
\pm SD	11.2	6.6	22.3	11.8	11.8	7.9

P* = Metoprolol + Placebo M** = Metoprolol + Molsidomine
BP*** = Blood Pressure

Table 2. Exercise tolerance

Treatment group	Before treatment			After two weeks			Improvement		
	Duration [s]	Max. load [W]	ST-depression [mm]	Duration [s]	Max. load [W]	ST-depression [mm]	Duration [s]	Max. load [W]	ST-depression [mm]
<i>Metoprolol +</i>									
<i>Placebo</i>									
Median	335	100	2.0	325	90	1.0	15	0	-1.0
Range	180, 960	50, 200	0.0, 5.0	45, 630	50, 160	0.0, 4.0	-640, 255	-120, 50	-4.0, 1.0
<i>Molsidomine</i>									
Median	240	80	2.0	345 ^a	100 ^a	1.0	105	10	-0.75
Range	70, 390	50, 110	0.0, 6.0	180, 750	60, 130	0.0, 3.5	-90, 525	-10, 60	-0.6, 0.0

^a Significantly better than before treatment ($p < 0.05$; Wilcoxon matched-pairs signed-ranks test)

table in respect of height, weight and severity of angina.

All patients were hospitalized for at least 2 weeks according to the protocol. Only 7 patients remained in hospital for the entire 4-week period: 5 in the group with molsidomine and 2 in the group receiving placebo.

Due to this imbalance in the proportion of hospitalized patients in the two treatment groups, analysis of data was restricted to the first 2 weeks of the study. Both the frequency of anginal attacks and the consumption of nitroglycerin tablets remained almost stable during the period; there was no significant difference between the groups. The drug was well tolerated and no significant side effects were noticed during molsidomine therapy.

In both groups at the end of the study approximately half the patients stated that they had felt a moderate or marked improvement. The impression of the physician paralleled that of his patients.

Exercise Test Results

Heart rate, systolic and diastolic blood pressure values during rest, maximum exercise and 6 min post-exercise are shown in Table 1. There was no significant difference between the placebo and molsidomine groups in these parameters. The ST segment depression at maximal exercise was also similar in both groups. There was a tendency towards a mild improvement in exercise performance in the molsidomine-treated group (Table 2). During the period of hospitalization both the duration and the maximum load attained during exercise were slightly increased in the group receiving molsidomine. The median work load increased from 80 to 100 W and the median exercise duration from 240 to 345 s after treatment for 2 weeks.

By contrast, the placebo group started at a higher level of work load and exercise duration, i.e. 100 W and 335 s respectively. After 2 weeks, however, the work load had decreased to 90 W and the duration to 325 s. The difference between the 2 groups was not statistically significant.

Discussion

The aim of the study was to investigate whether a combination of a beta blocking agent, metoprolol, and molsidomine was effective and well tolerated.

The combination of a beta-blocker with a calcium antagonist may result in subjective and objective improvement in patients with chronic stable angina pectoris. However, the interaction between these drugs may lead to a fall in blood pressure, AV conduction disturbances and a strong negative inotropic action on the left ventricle (Deanfield et al. 1983; Opie and White 1980; Robson and Vishwanath 1982; Majid et al. 1980). These adverse effects may even lead to discontinuation of the combination.

With regard to long-acting nitrates, hypotension may lead to the same result (Opie and White 1980). Apart from this interaction effect on blood pressure, nitrates themselves can cause severe headaches. Another important problem is the relatively short duration of the nitrate effect.

In many respects molsidomine resembles nitrates in its action. The effectiveness of molsidomine in relieving myocardial ischaemia is also dependent on its peripheral vasodilator property. The vasodilation occurs predominantly by a direct action on the veins, resulting in venous pooling, thereby reducing the preload of the heart. As a consequence there is a decrease in pulmonary wedge pressure and in left ventricular end-systolic and end-diastolic pressures and volumes, leading to a reduction in the myocardial oxygen demand.

A direct arteriolar action of the drug has also been noted, by which it lowers the systemic vascular resistance (Majid et al. 1980). The latter action, however, only appears to be of importance during exercise.

In view of the possible disadvantages of the combination of beta blockers with calcium antagonists or longacting nitrates, an important advantage of molsidomine is that it has no effect on myocardial contractility, heart rate or blood pressure. This view is supported by the present findings during the exercise test. There was no difference in blood pressure or heart rate between the patients taking metoprolol with a placebo and those on metoprolol and molsidomine.

The anti-anginal effect of molsidomine as a single therapy and the improvement it produces in exercise capacity has already been noted.

The lack of a significant improvement here is probably due to the study population selected; i.e. patients who did not respond adequately to beta-blockers alone or in combination with long acting nitrates. Furthermore, a variable dose was not used.

Exercise duration and work load, however, showed a slight improvement in the molsidomine group, which might be of clinical importance.

Although a significant improvement could not be demonstrated for the combination of metoprolol and molsidomine compared to metoprolol and a placebo, adverse effects did not occur and the combination was well tolerated.

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J. P. van Mantgem, M. D., Ph. D.
Nachtwachlaan 435
NL-1058 ER Amsterdam
The Netherlands