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Acute Double Blind Trial of a New Anti-anginal Drug: Molsidomine

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Summary. The antianginal activity of Molsidomine, a recently developed compound, was studied in 6 patients with stable angina pectoris who attended 3 trial sessions. On different days the patients received single doses of Molsidomine (M; 2 mg), isosorbide dinitrate (ISDN; 5 mg) or placebo (P), in a double blind cross-over manner. All patients performed exercise tests at time 0 (before medication) and 30, 60, 120, 240 and 360 min after drug intake. Tests were performed on a treadmill using the Bruce protocol; the ECG were recorded on 3 channel equipment and was stored on 2 channel magnetic tape (Holter system). No difference between basal values before treatment and on exercise during placebo were observed. At a similar submaximal workload after M and ISDN there was no significant change in heart rate or pressure-rate product, a decrease in systolic blood pressure, a reduction of ST ischemic response between 30 to 120 min after drug intake, and after M alone, a significant decrease in diastolic blood pressure during the 6 hour period. Molsidomine produced clear inhibition of exercise-evoked ischemic ST changes and a long-lasting effect on diastolic blood pressure.

Key words: Molsidomine, isosorbide dinitrate, angina, ECG analysis, diastolic blood pressure.

The efficacy of an anti-anginal compound can be adequately assessed by an acute, single dose study using repeated stress testing [1]. The reproducibility of exercise tests repeated at hourly intervals has previously been demonstrated by Roskamm [2].

The present study was undertaken to examine the action profile of a new drug Molsidomine (M) in comparison with isosorbide dinitrate (ISDN) and placebo (P) in patients with angina pectoris. Molsidomine (N-ethoxycarbonyl-3-morpholinosydnonimine; Fig. 1) is a recently developed drug that was considered likely to be efficacious in angina pectoris because of its pharmacological properties [3]. The drug produces a reduction in myocardial oxygen consumption by decreasing venous return and systolic blood pressure [4, 5]. The action of M begins 10 min after oral ingestion, and even earlier when administered sublingually, and lasts 5 to 7 h.

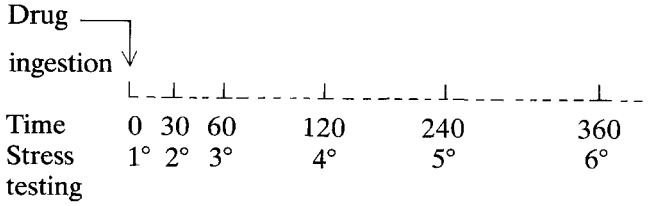
Material and Methods

a) Patient Selection. Six male patients with stable angina pectoris were studied; age range 43 to 65 years, weight 70 to 90 kg and height 1.67 to 1.76 m. All of them had had definite electrocardiographic evidence of myocardial ischemia during and/or after an exercise stress test.

Two patients had suffered myocardial infarction. Selective coronary angiography in a third patient showed 90% stenosis of the circumflex artery and hypokinesia of the lateral wall of the left ventricle. All the patients had been engaged in a cardiac rehabilitation program for six months or more and had not received any kind of medication since then.

b) Method. The design used was a double blind cross-over technique. Each patient attended 3 trial sessions, one every day, randomly allocated to either of the treatments. Stress testing was performed according the multistage treadmill technique recommended by Bruce [6].

1. Scheme of each session



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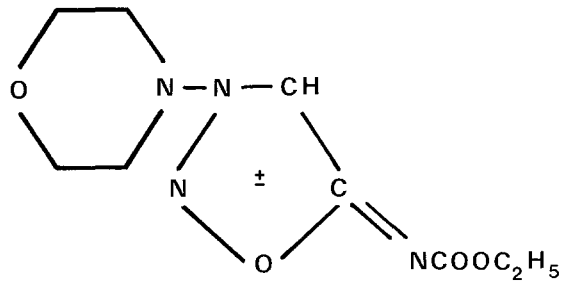

$C_9H_{14}N_4O_4$

Fig. 1. Molsidomine; structural formula

2. Details of the Tests

a) All drugs were given sublingually after completion of the first test.
b) After the third test the patient was given tea with sugar
c) During the intervals the patients remained at relative rest in a comfortable room
d) In test 2°–6° patients commenced at Stage III of Bruce's treadmill technique (speed 1.7 miles/h and 10% gradient)
e) The initial test before treatment was continued until the development of fatigue. The subsequent test was stopped when ST depression of 2 mm was detected by the digital computer (see "Equipment"). This point was conventionally called "final workload".

3. Parameters

- Heart rate (HR)
- Systolic blood pressure (SBP)
- Diastolic blood pressure (DBP)
- Mean arterial pressure (MAP)
- Pressure x rate product (MTTI[1])
- ST depression
- Total working time
- Symptoms

4. Drug Administration

- Molsidomine: 2 mg tablet in a single dose was administered sublingually
- Isosorbide dinitrate: single dose of 5 mg taken sublingually [7, 8, 9]
- Placebo and active preparations were identical in size, shape and colour.

5. Equipment

A treadmill (Avionics) was used connected to a 3-channel oscilloscope, an ECG recorder and a digital computer of time, HR and ST. Two of the oscilloscope channels were connected to a magnetic tape recorder (Holter system) for analysis later in a high speed scanner. High speed recording of the ECG permitted production of "trend" graphs of heart rate and ST segment. The ECG leads used were: MV_3 (sternum to V_3), MV_5 (sternum to V_5) and ML_1 (sternum to first lumbar vertebrae). ST depression was computed from the MV_5 channel.

6. Evaluation

The data obtained were evaluated for the submaximal and final workload attained. Submaximal workload was defined as the stage completed by each patient immediately before the final stage, when a 2 mm ST depression appeared. This level of effort was used to assure more correct assesment of treatments. In each patient the same submaximal workload was used for comparison between drugs. At this level of work the different parameters for each time during drug treatment were compared with the basal values. The statistical methods employed were variance analysis with block separation [10], Tuckey test [11] for the basal values at rest, and Dunnet's test [11]. The possibility of gaining stages and the total time of effort was evaluated by the t-test.

Results

The mean value of each parameter before and after treatment is shown in Table 1. A global standard deviation for each parameter was obtained by variance analysis.

No difference between the mean value at rest for each of the variables was detected using the Tuckey test ($p > 0.05$). Placebo administration did not cause a significant change in any of the parameters analyzed. Heart rate and MTTI showed no significant change at rest or at submaximal workload after M and ISDN. However, a tendency to decrease in MTTI during both active drug periods was observed. Systolic blood pressure, measured at submaximal effort, was significantly reduced 60, 120, 240 and 360 min after the administration of M 2 mg. A decrease in SBP was also observed 120, 240, and 360 min after ISDN (Table 1).

A long lasting effect on exercise diastolic blood pressure (Fig. 2) was seen after M (60 to 360 min after drug intake). A systematic reduction of exercise DBP after M 2 mg, from 104 mmHg before treatment to 75 mmHg after 6 h ($p < 0.01$), was also noted. No significant alteration of DBP after ISDN was observed.

[1] MTTI: modified tension – time index

Table 1. Mean values

Parameter	Drug	At rest	Basal	Time (min)				
				30	60	120	240	360
HR	M	74.3	121.0	121.1	125.3	123.6	122.1	124.0
beats/min	I	74.8	123.6	126.8	130.6	128.5	125.6	125.6
SD = 7.95	P	74.8	116.6	119.5	120.6	122.3	120.5	121.1
SBP	M	135.0	180.0	160.0	155.0*	150.0**	151.6**	155.0*
mm Hg	I	145.0	185.0	165.0	168.3	157.5**	161.6*	161.6*
SD = 14.07	P	141.6	160.0	160.0	165.0	158.3	171.6	166.6
DBP	M	86.6	104.1	90.0	85.0*	83.3**	80.0**	75.0**
mm Hg	I	91.6	96.7	85.0	83.3	85.0	85.0	86.6
SD = 11.46	P	91.6	96.6	95.0	100.0	88.3	90.0	94.1
MAP	M	102.7	129.4	113.3*	108.3**	105.5**	103.8**	101.6**
mm Hg	I	109.4	126.1	111.6*	111.6*	109.1**	110.5*	111.6*
SD = 8.97	P	108.3	117.7	116.6	121.6	111.6	117.2	118.3
MTTI	M	99.7	218.9	194.0	194.5	186.5	185.2	194.0
	I	108.7	228.2	210.1	221.0	202.3	204.9	202.3
SD = 23.86	P	105.1	187.3	192.7	199.9	194.8	206.4	202.3
ST	M	−0.26	−1.18	−0.55**	−0.53**	−0.55**	−0.93	−1.00
mm	I	−0.31	−1.41	−0.65**	−0.65**	−0.66**	−0.96	−1.05
SD = 0.33	P	−0.35	−0.98	−0.98	−0.91	−0.85	−0.85	−0.98

I: ISDN; * $p<0.05$; ** $p<0.01$

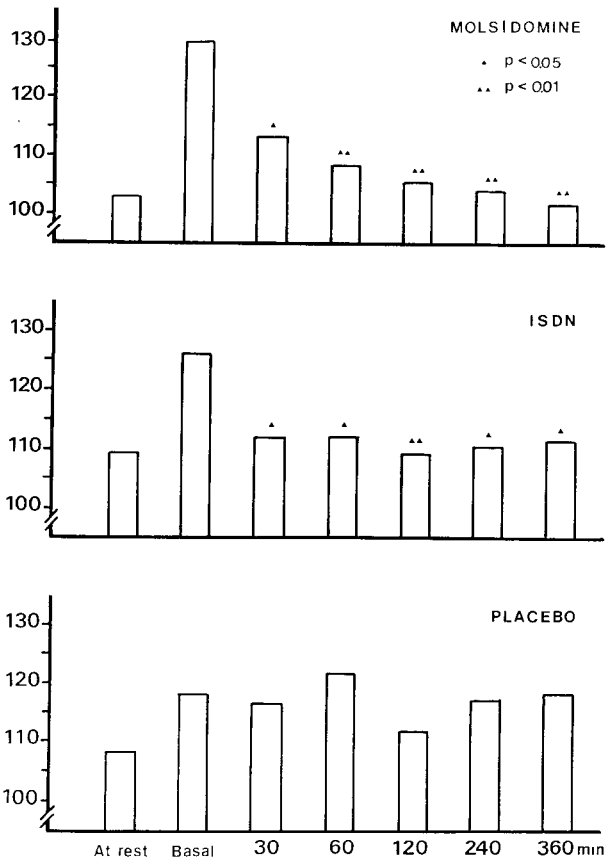

Fig. 2. Diastolic blood pressure (mmHg) at rest and during exercise at a similar workload after administration of single doses of Molsidomine, ISDN or placebo

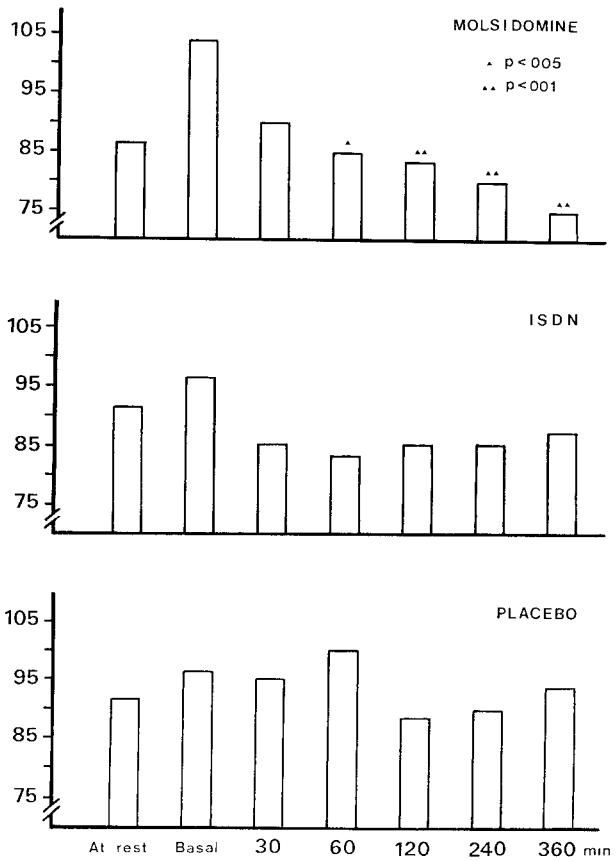

Fig. 3. Mean arterial pressure (mmHg) at rest and during exercise at similar workloads after administration of single doses of Molsidomine, ISDN or placebo

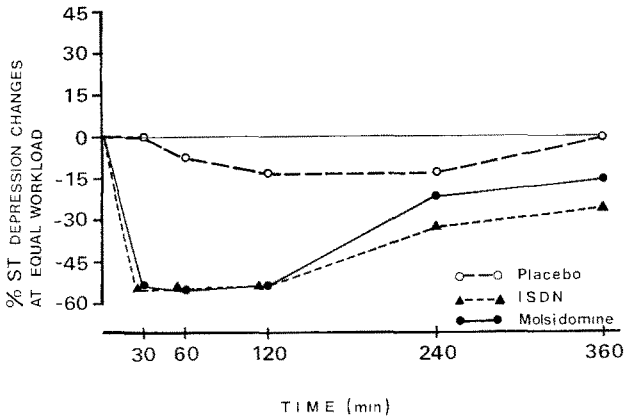

Fig. 4. ST segment depression at similar workloads after single doses of Molsidomine, ISDN and placebo. Percentage modications of the ischemic response was calculated in relation to basal values during exercise

Mean arterial pressure was reduced by both drugs during the tests. The effect of M was more consistent and long-lasting (Fig. 3).

A significant inhibition of the ischemic response – ST segment depression – at a similar submaximal workloads was observed after M and ISDN, 30, 60 and 120 min after drug intake. Percentage changes in the ST segment are shown in Figure 4.

In spite of improvement in certain individuals, final workload was not changed by either drug, considering both gain in stages and time of effort.

Side effects were few and mild; headache during the first hour after ingestion was noted in two patients (one after ISDN and the other after M). A single patient showed a transient fall in SBP, down to 85 mmHg and accompanied by dizziness, 60 min after ISDN.

Discussion

Basal values of HR, SBP, DBP, MAP, MTTI and ST before drug administration and during the placebo sessions were very stable, in agreement with the previous report by Roskamm [2] about the reproducibility of stress testing. He performed repeated tests on the same day in cases of angina pectoris and found that maximal workload was almost a constant for the individual patient. Our findings have confirmed Roskamm's observations and suggest that HR, SBP, DBP, MAP, MTTI and ST also have very good reproducibility in repeated tests.

ISDN and the new drug Molsidomine had an almost similar inhibitory action on the ischemic response at a given workload. However, a clearer effect on arterial blood pressure was observed after M 2 mg. Mean arterial pressure was decreased significantly 30 min ($p<0.05$) after M and the fall was more marked at 360 min ($p<0.01$).

Molsidomine caused a reduction in DBP ($p<0.05$) 60 min after sublingual ingestion, which was more pronounced at 360 min ($p<0.01$). On the other hand, no change in DBP after ISDN was noted. In the present study the hypotensive effect of M lasted for 6 h after sublingual administration, and it would have had, therefore, a sustained action on cardiac afterload.

The lack of alteration in total working time could be explained on the basis of patient selection. The group was engaged in a vigorous rehabilitation programme, so no gain in maximal physical capacity could be expected after drug treatment. In a very recent report [12] about peroral M administration, an increase in maximal work capacity in pressumably "non-trained" patients was noted.

It can be concluded that the new anti-anginal drug Molsidomine produced a net inhibition of the exercise-evoked ischemic response, as well as a long-lasting hypotensive effect.

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