Long-lasting Effect of Oral Molsydomine on Exercise Performance

A New Antianginal Agent

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SUMMARY This study examines whether the beneficial effects of molsydomine, a recently introduced antianginal agent, on exercise performance of patients with angina pectoris are long lasting. The hemodynamic effects are known to persist for several hours. The effects of molsydomine on the duration of exercise and the time to the onset of ST depression were compared to those of placebo during two hours after oral administration. Molsydomine prolonged the duration of exercise in all eight patients (average 2.8 min, \( P < 0.001 \)) and delayed the onset of ST depression (average 2.2 min, \( P < 0.001 \)), while the placebo failed to alter these measurements. The increment of the duration of exercise produced by 2 mg of molsydomine in two hours following oral administration was comparable to the increment produced in a few minutes after 0.3 mg of nitroglycerin given sublingually. The results indicate that molsydomine offers prophylaxis for angina pectoris that lasts at least two hours after oral administration.

EFFORTS TO ACHIEVE LONGER THERAPEUTIC ACTION of drugs used in the prevention of angina pectoris have resulted in the introduction of a variety of nitrate preparations. Whether they offer truly long-lasting benefits in comparison with nitroglycerin still remains controversial.1-7

Molsydomine (N-ethoxycarbonyl-3-morpholinosydnonimine), a recently introduced antianginal agent, exerts hemodynamic effects similar to those of nitroglycerin, 8 but its effects are characteristically longer-lasting. 8-10 Molsydomine can be given orally since hemodynamic effects exerted by an oral administration of this agent were similar to those obtained with sublingual administration.10

Persistence of hemodynamic changes, however, may not be always correlated with a similar persistence of beneficial action on exercise capacity.3 The efficacy of a drug in the prevention of angina is best evaluated by an acute study using a protocol with multistaged exercise tests.11 The present study was undertaken to examine the exercise performance of patients with angina pectoris during the two hours after oral administration.

Materials and Methods

Eight patients were studied. Criteria for inclusion in this study were 1) definite electrocardiographic evidence of myocardial ischemia during or after exercise stress testing; 2) presence of definable end-point of ischemia during exercise with typical angina pain; 3) absence of evidence of valvular heart disease, congestive heart failure, recent myocardial infarction or recent change in the frequency or severity of angina; 4) no history of taking digitalis for at least six weeks prior to the study.

Patients ranged in age from 51 to 71 years old (mean 60 years old). All of them were male. The history of exertional angina pectoris had been present for from two months to five years prior to the study. No patient had a history of myocardial infarction. Selective coronary cineangiography was not performed in any patient in this series. Nonspecific ST-T changes were present on resting ECGs in three patients. There was no evidence of previous myocardial infarction or conduction abnormality such as bundle branch block on the electrocardiograms.

The patients were hospitalized and all cardiovascular medications were stopped except for nitroglycerin as needed. Prior to the definitive studies all patients had had exercise stress testings on at least two different days. Patients exercised on treadmill until the onset of angina, at which time patients stopped exercising. The test began with the patient walking at 1.7 mph on a 10% grade with the speed and grade increased every three minutes according to the following protocol.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Speed</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.7 mph</td>
<td>10%</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>3.4</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>4.2</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>5.0</td>
<td>18</td>
</tr>
</tbody>
</table>

These preliminary studies were done to familiarize patients with testing procedures and to test reproducibility of exercise performance.

On the day of the definitive investigation, the patients were studied in a fasting state in a warm room. They had neither smoked nor taken nitroglycerin the preceding three hours. The exercise protocol was designed following Redwood et al.11 The load on a treadmill was increased every three minutes until angina occurred. The initial workload was chosen so that each patient experienced angina during three to six minutes of exercise (the second level). The electrocardiogram was monitored continuously using the manubrial-CM 5 bipolar lead. Electrocardiographic evidence of ischemia was defined as flat or downsloping ST-segment depression of 0.5 mm or more.
was considered to be ischemic if ST more
than
lasting at least 0.08 sec.12 When ST segment is upsloping, it
was considered to be ischemic if ST depression is more than
1 mm at 0.08 sec after the J junction.13 However, all patients
developed either flat ST depression of 1 mm or more or
more than 2 mm depression at 0.08 sec after J point when
ST segments were upsloping, during or immediately after
exercise. In patients with depressed ST segments in the
resting tracings, a further depression of at least 0.5 mm was
considered as an abnormal response to exercise stress.14
Blood pressure was measured every one minute during exercise
and immediately after the cessation of exercise using an
automatic sphygmomanometer.14

The definitive investigations were done on three different
days, either three consecutive days or every other day for
five days. On each test day the patient underwent control ex-
ercise in two hours after breakfast. On the first and second
test day molsydomine 1 tablet (2 mg) or placebo was given
orally at the end of the control study and two hours later
the patient exercised again. If molsydomine was given on the
first day, placebo was used on the second day and vice versa.
The sequence of molsydomine and placebo was randomized.
All exercise tests were conducted by one of the authors
(A.T.) who was not told which of the tablets had been
given to the patient. On the third test day, the effect of
nitroglycerin on exercise performance was studied. After 20
minutes of rest following control exercise, nitroglycerin (1
tablet 0.3 mg) was given sublingually and exercise was
repeated in three minutes.

Analysis of the statistical significance of differences
observed in heart rate, blood pressure, pressure-rate
products, the time to the onset of angina and ST depression
between before and after treatment with placebo,
molsydomine or nitroglycerin, or between placebo and
molsydomine was performed using the paired t-test.

Results

Reproducibility of Exercise Performance

Reproducibility of the study was examined by comparing
the results between three control exercises, which were per-
formed on each test day before drug treatment. Heart rate,
systolic blood pressure, pressure-rate products before ex-
ercise and at the onset of angina as well as the time to the onset
of angina and ST depression in control exercises are sum-
marized in table 1. Values before exercise were obtained
with the patient standing. None of these measurements was
significantly different between any two test days, indicating
that patient’s condition before control exercise was similar
on each test day and exercise performance was reproducible.

Effects on Exercise Capacity and ECG Changes

The effect of molsydomine on exercise capacity in two
hours after oral administration was evaluated by comparing
the duration of exercise the patient could perform before
the onset of angina following an administration of molsydomine
to that after placebo (fig. 1). After molsydomine the patients
exercised an average of 7.3 ± 0.3 min before the onset of
angina, which was 2.8 minutes longer as an average than the
duration of exercise the patient could tolerate in control ex-
ercise done on the same day. After placebo the patients ex-
ercised 4.8 ± 0.2 minutes which was not different from the
duration of exercise in the control study. The difference in
the duration of exercise (the time to the onset of angina)
between molsydomine and placebo was statistically signifi-

![Figure 1. Effects of placebo and molsydomine on the duration of exercise before the onset of angina. The circle and bars on either side of the panel indicate the mean ± se. Dashed horizontal lines indicate three-minute interval levels of workload. Placebo did not increase the duration of exercise. In contrast molsydomine increased it by an average of 2.8 min. After molsydomine all patients were able to exercise against a greater load by one stage.](http://circ.ahajournals.org/)

<table>
<thead>
<tr>
<th>Days</th>
<th>HR (beats/min)</th>
<th>SBP (mm Hg)</th>
<th>HR × SBP (beats/min) × (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73.7 ± 3.3</td>
<td>125.6 ± 3.6</td>
<td>8445.6 ± 574.8</td>
</tr>
<tr>
<td>2</td>
<td>76.4 ± 4.0</td>
<td>121.9 ± 7.3</td>
<td>8851.2 ± 536.4</td>
</tr>
<tr>
<td>3</td>
<td>73.6 ± 3.4</td>
<td>121.3 ± 5.1</td>
<td>8561.2 ± 667.8</td>
</tr>
</tbody>
</table>

Each value indicates the mean ± se.

There is no significant difference between any two test days in any of heart rate, systolic blood pressure, pressure-rate products at rest or at the onset of angina, or of the duration of exercise before the onset of angina or ST depression.

Abbreviations: HR = heart rate; SBP = systolic blood pressure; ST = ST depression.

![Table 1. Exercise Performance in Exercise Control State](http://circ.ahajournals.org/)
cant \( P < 0.001 \). After molsydomine all patients were able to exercise against a greater load by one stage (fig. 1).

On seven patients with ischemic changes appearing in the monitored lead during exercise, the time to the onset of ST depression as defined in methods was compared (fig. 2). Placebo did not prolong the time to the onset of ST depression, but a delay in the time of these changes, by 2.2 min on the average, was noted in all patients after molsydomine \( (P < 0.001) \). An example of the delay of the onset of ST depression produced by molsydomine is shown in figure 3. The ST segment was depressed after four minutes of exercise in the control study while a similar degree of ST depression was not observed until after six minutes of exercise following molsydomine.

Exercise capacity was increased by nitroglycerin in all patients (fig. 4). The average increase of the duration of exercise was 3.3 minutes \( (P < 0.001) \). The patients exercised to a workload at least one stage greater after nitroglycerin in control exercise (fig. 4). Subjective improvement in exercise performance after nitroglycerin was accompanied by a delay in the onset of ST depression on the electrocardiograms (fig. 4).

**Effects on Hemodynamic Changes during Exercise**

Hemodynamic changes before and during exercise produced by placebo, molsydomine and nitroglycerin are summarized in table 2 and shown in figure 5 and figure 6. Values before exercise were obtained with the patient standing. Heart rate, systolic blood pressure, and pressure-rate products before exercise and at the onset of angina were not different between control exercise (shown in table 1) and exercise after placebo.

Systolic blood pressure before exercise was lower \( (P < 0.01) \) and heart rate was higher \( (P < 0.05) \) following molsydomine and nitroglycerin in comparison to those after placebo (table 2, fig. 5 and fig. 6). Changes in heart rate and systolic blood pressure were comparable between molsydomine and nitroglycerin. Thus 2 mg of molsydomine in two hours after oral administration exerted hemodynamic changes at rest similar to those noted in a few minutes following 0.3 mg of nitroglycerin given sublingually.

Hemodynamic changes during exercise were compared after the same duration of exercise (three minutes of exercise) and at the onset of angina (fig. 5 and fig. 6). After three minutes of exercise systolic blood pressure was lower following nitroglycerin \( (P < 0.05) \) and tended to be lower following molsydomine \( (0.05 < P < 0.1) \) than they were after placebo. However heart rate was not significantly higher following either drug. At the onset of angina, which occurred at the average of 4.8, 7.3, and 7.9 min of exercise with placebo, molsydomine and nitroglycerin respectively, systolic blood pressure was not different between the three, but heart rate was higher following nitroglycerin and molsy-
Table 2. Effects of Placebo, Molsydomine, or Nitroglycerin on Circulatory Changes before and during Exercise

<table>
<thead>
<tr>
<th>Pt</th>
<th>Drug</th>
<th>Duration Ex (min)</th>
<th>SBP (mm Hg)</th>
<th>HR × SBP (beats/min-mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Heart Rate (beats/min)</td>
<td>Before Ex</td>
<td>During Ex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 min</td>
<td>6 min</td>
<td>At AP</td>
</tr>
<tr>
<td>Y.A.</td>
<td>P</td>
<td>4.9</td>
<td>69 87 — 76</td>
<td>110 125 — 130</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>7.1</td>
<td>83 98 98 102</td>
<td>95 110 125 135</td>
</tr>
<tr>
<td></td>
<td>NG</td>
<td>9.7</td>
<td>82 97 98 105</td>
<td>100 120 130 135</td>
</tr>
<tr>
<td>S.M.</td>
<td>P</td>
<td>5.3</td>
<td>63 100 — 108</td>
<td>150 175 — 175</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>6.8</td>
<td>76 105 120 125</td>
<td>125 165 175 175</td>
</tr>
<tr>
<td></td>
<td>NG</td>
<td>8.3</td>
<td>83 107 120 115</td>
<td>110 150 165 170</td>
</tr>
<tr>
<td>S.Y.</td>
<td>P</td>
<td>5.1</td>
<td>58 69 — 78</td>
<td>130 135 — 150</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>7.3</td>
<td>68 73 79 88</td>
<td>120 135 135 145</td>
</tr>
<tr>
<td></td>
<td>NG</td>
<td>8.0</td>
<td>63 72 80 96</td>
<td>125 140 150 160</td>
</tr>
<tr>
<td>T.I.</td>
<td>P</td>
<td>4.5</td>
<td>92 110 — 123</td>
<td>135 165 — 190</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>8.7</td>
<td>89 92 105 128</td>
<td>115 135 135 175</td>
</tr>
<tr>
<td></td>
<td>NG</td>
<td>8.5</td>
<td>97 109 109 130</td>
<td>100 130 145 175</td>
</tr>
<tr>
<td>S.N.</td>
<td>P</td>
<td>5.0</td>
<td>65 73 — 81</td>
<td>140 145 — 160</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>7.6</td>
<td>79 83 98 102</td>
<td>140 155 165 170</td>
</tr>
<tr>
<td></td>
<td>NG</td>
<td>8.6</td>
<td>68 86 93 105</td>
<td>120 135 160 170</td>
</tr>
<tr>
<td>F.A.</td>
<td>P</td>
<td>5.7</td>
<td>68 93 — 108</td>
<td>110 145 — 160</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>7.0</td>
<td>77 94 115 130</td>
<td>100 140 165 165</td>
</tr>
<tr>
<td></td>
<td>NG</td>
<td>7.5</td>
<td>63 97 115 121</td>
<td>105 135 160 165</td>
</tr>
<tr>
<td>M.S.</td>
<td>P</td>
<td>3.9</td>
<td>87 120 — 128</td>
<td>125 150 — 150</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>6.1</td>
<td>89 127 145 148</td>
<td>105 140 165 165</td>
</tr>
<tr>
<td></td>
<td>NG</td>
<td>6.1</td>
<td>97 130 138 155</td>
<td>105 140 170 170</td>
</tr>
<tr>
<td>S.I.</td>
<td>P</td>
<td>3.8</td>
<td>74 93 — 96</td>
<td>120 140 — 145</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>7.5</td>
<td>65 88 98 100</td>
<td>95 125 130 150</td>
</tr>
<tr>
<td></td>
<td>NG</td>
<td>7.0</td>
<td>74 94 108 120</td>
<td>110 130 135 135</td>
</tr>
<tr>
<td>Mean ± se P</td>
<td>4.8</td>
<td>71.8 93.1 — 99.8</td>
<td>127.5 147.5 — 137.5</td>
<td>9131.9 15901.2</td>
</tr>
</tbody>
</table>

*P < 0.05 (molsydomine or nitroglycerin vs placebo)
**P < 0.01 (molsydomine or nitroglycerin vs placebo)
***P < 0.001 (molsydomine or nitroglycerin vs placebo)

P, M and NG indicate placebo, molsydomine, and nitroglycerin respectively. Ex = exercise; AP = angina pectoris.

Discussion

Our results indicate that molsydomine, N-ethoxy-carbonyl-3-morpholinosydnonimine (SIN-10), produced a significant increase in exercise capacity in all patients in two hours after oral administration. Subjective improvement was accompanied by a delay in the onset of ischemic electrocardiographic changes.

The therapeutic efficacy of a drug in the prevention of angina is best evaluated by an acute study using a protocol of multistage exercise.11 In order to evaluate drug effects on exercise performance properly, the design of the protocol is important. The protocol should be able to demonstrate the reproducibility of exercise performance without a therapeutic intervention, and should be sensitive enough to reveal the benefit of a drug on exercise capacity, which is known to be effective in the prevention of angina. Redwood et al. have shown that if progressive workloads that cause angina in 3 to 6 min in the control study are chosen, exercise performance is reproducible during repetitive exercises and the protocol is particularly sensitive in identifying altera-

Figure 4. Effects of nitroglycerin on the duration of exercise and the time to the onset of ST depression. Dashed lines indicate the three-minute levels of workload. Nitroglycerin increased the duration of exercise by an average of 3.3 min and delayed the onset of ST depression by 2.7 min.
tions in exercise capacity produced by a therapeutic intervention.\textsuperscript{11} In the present study the initial workload was chosen as suggested by Redwood et al. so that each patient developed angina in 3 to 6 min of exercise in the control study. Reproducibility of exercise performance was demonstrated by the absence of difference in exercise performance between any two control studies, which were performed on each test day before drug treatment. Since placebo failed to produce any difference in the duration of exercise or the time to the onset of ischemic changes appearing on the electrocardiograms, improvements observed after molsydomine were not due to the training or placebo effect.

The results in the present study suggest that molsydomine is very effective as a drug prescribed for the symptomatic prophylaxis of angina pectoris, since its beneficial effects in the prevention of angina last at least two hours after oral administration. A variety of nitrate preparations have been introduced to achieve more prolonged therapeutic action, some with altered molecular structure and others with altered route of administration, but it is now recognized that none of sublingual nitrates offers really long-lasting effects,\textsuperscript{1}

and oral administration of nitrates is ineffective\textsuperscript{6} or produces an inconsistent improvement\textsuperscript{4} in contrast to the unequivocal improvement following the same drug given sublingually. Although the present study was not primarily designed to compare between the effects of molsydomine and of nitroglycerin, the effect on exercise capacity of 2 mg of molsydomine in two hours after oral administration was comparable to that observed in a few minutes following 0.3 mg of nitroglycerin given sublingually. The latter result, however, does not necessarily indicate that the antianginal effects of the two drugs are equal since only one dose of the drug was studied to compare.

Molsydomine was recently synthesized by Masuda et al.\textsuperscript{18} and has a long lasting hypotensive effect.\textsuperscript{8,10} The hypotensive effects of molsydomine appear to be produced by vasodilatation of capacitance vessels because, following intravenous administration, pulmonary arterial blood flow as well as superior and inferior vena caval flow decreased in accordance with hypotension,\textsuperscript{9} and little vasodilatation of resistant vessels was noted.\textsuperscript{19} However this assumption is not yet conclusive since there has been no study done relating to the direct effects of molsydomine on venous volume. Molsydomine has no sympatholytic, parasympathomimetic, ganglion blocking or cardiac depressing actions.\textsuperscript{9,10}

These cardiovascular effects of molsydomine seem to be largely produced by its metabolites, since in hepatectomized or carbon tetrachloride-treated animals molsydomine exerted either no hypotensive effect or markedly reduced effects with a delay of the onset of action whereas
metabolites retained its full hypotensive effects in those animals. Molsydomine is shown to be metabolized by hepatic enzymes to 3-morpholininosydnoine (SIN-1), which is transformed nonenzymatically to N-nitroso-N-morpholinoacetoniitire (SIN-1A) in blood. Both SIN-1 and SIN-1A are biologically active and retain hypotensive effects. Vasodilating effects of SIN-1A resemble those of nitroglycerin not only quantitatively but also qualitatively, effective both in capacitant as well as resistant vessels, rapid in the onset of action but transient, while those of molsydomine are slowly induced but long-lasting. It is suggested that the differences in the onset and the duration of action of these compounds are due to the different rate of release of active principle. Molsydomine is slow in the onset of action and long-lasting presumably because it has to be metabolized to the active forms to produce the effects.

Oral administration of molsydomine exerts as potent hypotensive effects as sublingual administration of this agent. After oral administration of 2 mg of molsydomine hypotensive effects in patients may last as long as 6 hours. It is reported in the experimental study that molsydomine is easily absorbed from small intestine with about a half of the oral dose being absorbed during the first 30 minutes.

The way molsydomine works against angina in patients is not known. We examined hemodynamic changes at rest standing and during exercise produced by 2 mg of molsydomine in two hours after oral administration and compared them to changes observed a few minutes after 0.3 mg of nitroglycerin given sublingually. Changes in heart rate, systolic blood pressure, and pressure-rate products at rest and during exercise were similar between these two drugs (fig. 5 and fig. 6). These results may suggest that the antianginal effects of molsydomine are produced in the similar way to those of nitroglycerin. Treatment with these drugs were associated with reduced systolic blood pressure and increased heart rate at rest, and with reduced or a tendency for reduction in systolic blood pressure during exercise in comparison to those with placebo. At the onset of angina systolic blood pressure after drugs was similar to that after placebo but heart rate was higher, resulting in higher pressure-rate products after drugs.

The result that heart rate after the same duration of exercise was not significantly higher following nitroglycerin or molsydomine than that after placebo in spite of a fall of blood pressure is somewhat different from the result previously reported by Goldstein et al. The difference between our study and that reported by Goldstein et al. may be due to the different dose of the drug used and the different group of patients examined. The reduction of blood pressure during exercise produced by the drugs was less in our study than that reported by Goldstein et al. In our study, although changes were not statistically significant as a group, heart rate was higher in seven of eight patients following nitroglycerin and six of eight patients following molsydomine than that was after placebo (table 2). If the larger doses of the drugs were chosen with more reduction of blood pressure, significantly higher heart rate might have been noted following drugs than after placebo. In addition, the patients in our study were older than those studied by Goldstein et al. It is reported that baroreflex sensitivity in respect to reflex heart rate control is reduced as age increases. It is also known that exercise is associated with reduced baroreflex sensitivity. The latter may explain the less dramatic increase of heart rate during exercise than at rest in response to a fall of blood pressure. It is reported in the experimental study that molsydomine does not alter baroreflex.

In addition to the reducing effect on myocardial oxygen consumption by venous pooling, nitroglycerin may work against angina by redistributing regional myocardial blood flow favorably to the ischemic area. Molsydomine may also affect the distribution of regional myocardial blood flow in the presence of chronic myocardial ischemia. Pressure-rate products at the onset of angina, which are often used as the index of myocardial oxygen consumption, were higher after molsydomine, as well as nitroglycerin, than they were after placebo. These results, however, do not imply that these two drugs increased myocardial oxygen delivery in these patients since other variables such as ejection time or ventricular size, which are also known to affect myocardial oxygen consumption, were not examined in this study. In the study of Goldstein et al., nitroglycerin increased pressure-rate products at the time of angina, but when these values were multiplied by ejection time the resulting triple products at angina were the same after nitroglycerin as they were after placebo.

Molsydomine might produce transient headache, facial flush, orthostatic hypotension, gastrointestinal symptoms such as nausea, vomiting, diarrhea, and loss of appetite. Molsydomine may not be given to patients with glaucoma since it can increase intra-ocular pressure. One of our patients complained of mild headache following an administration of 2 mg of molsydomine but no serious adverse effect was encountered.

Acknowledgment

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