LONG-TERM EFFECTS OF MOLSIDOMINE ON EXERCISE TOLERANCE IN PATIENTS WITH EXERTIONAL ANGINA PECTORIS

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Molsidomine is a derivative of the sydnonimines and is a long-acting vasodilator that may be effective in the treatment of chronic stable angina pectoris. To evaluate the therapeutic efficacy and drug tolerance, eight men with stable angina pectoris performed a symptom-limited maximal exercise test on a computer-assisted treadmill. After ingesting either placebo or molsidomine administered in single blind fashion 90 min before the exercise test on the first day of treatment, molsidomine decreased the average systolic blood pressure response from 154 ± 3 (SEM) to 135 ± 4 mmHg (p < 0.01). However it did not significantly change the average heart rate response (117 ± 7 to 124 ± 8 beats/min) and the rate-pressure product (18.1 ± 1.2 x 10^5 to 16.8 ± 1.1 x 10^3). The average time up to the onset of ischemia at which significant ST-segment deviation (0.1mV) first appeared was increased from 9.0 ± 1.7 to 12.8 ± 1.2 min (p < 0.001) after molsidomine. At peak exercise after molsidomine, the mean value of ST-segment deviation in V5 or aVF was decreased (p < 0.001). This result was obtained even though the average exercise duration was increased from 11.4 ± 1.7 to 13.6 ± 1.2 min (p < 0.001). The treadmill score according to Hollenberg was also improved from 47 ± 24 to 1 ± 14 after molsidomine administration. After six weeks of continued therapy with molsidomine the favorable effect on exercise tolerance was significantly decreased in terms of exercise duration, the time up to the onset of ischemia, and the treadmill score. The discontinuation of molsidomine treatment after six months' therapy did not deteriorate the exercise tolerance. Thus, molsidomine is effective in treating stable angina pectoris, but appears to possess a drug tolerance on long-term treatment.

Molsidomine (N-ethoxycarbonyl-3-amino-morpholine-sydnonimine, SIN-10) is an antianginal drug that was first synthesized and introduced into clinical use in Japan in 19701-4 and was later extensively studied in Europe5-10. Animal studies have shown that molsidomine reduces the ventricular preload as well as the afterload, and decreases myocardial oxygen consumption. These effects appear to be similar to those of the nitrates, however, they are much longer lasting than the latter after oral or sublingual administration2,3. Single oral administration of molsidomine was reported to increase exercise tolerance to the same extent as the sublingual administration of nitroglycerin11,12. Previous studies, however, have been done with respect to short-term effects13. The long-term efficacy and the potential drug tolerance have not been evaluated. The purpose of this study is

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TABLE I CLINICAL DATA IN EIGHT PATIENTS WITH EFFORT ANGINA

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs)</th>
<th>Prior MI</th>
<th>Coronary Angiography</th>
<th>Left ventriculography</th>
<th>EF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>LM LAD LCX RCA</td>
<td>Anterior Apical Inferior</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>60</td>
<td>(−)</td>
<td>– – – 99</td>
<td>N N HK</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>(−)</td>
<td>75 90 –</td>
<td>N N N</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>67</td>
<td>(+)</td>
<td>– 99 90 –</td>
<td>AK AK N</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>(+)</td>
<td>– – 99 99</td>
<td>N N HK</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>64</td>
<td>(−)</td>
<td>75 – –</td>
<td>N HK N</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>56</td>
<td>(−)</td>
<td>90 – –</td>
<td>HK N N</td>
<td>46</td>
</tr>
<tr>
<td>7</td>
<td>61</td>
<td>(−)</td>
<td>90 – –</td>
<td>N N N</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>(−)</td>
<td>75 – 100</td>
<td>HK N N</td>
<td>74</td>
</tr>
</tbody>
</table>

Abbreviations: MI = Myocardial infarction, LM = Left main, LAD = Left anterior descending, LCX = Left circumflex, RCA = Right coronary, EF = Ejection fraction, N = Normal, AK = Akinesis, HK = Hypokinesis

Fig. 1. The trendgram of ST segment deviation and ST slope in V_{5,6} and aVF in a patient 3. Exercise duration increased from 6.0 min before (Fig.1A) to 9.3 min after molsidomine administration (Fig.1B). Treadmill score improved from −135 before to −3 after the administration. The maximum ST segment depression was decreased from 2.5 mm in V_{5} and 3.8 mm in aVF before to 1.1 mm and 3.1 mm, respectively, after the administration. The vertical line in each trendgram indicates the end point of treadmill exercise.

to compare the acute effects of molsidomine with its long-term effects and to examine whether or not drug tolerance takes place.

METHOD

Subjects

Eight men with obstructive coronary artery disease and exertional angina pectoris entered into a single blind efficacy study. Clinical data and angiographic findings are summarized in Table I. At the completion of this acute trial, seven patients elected to continue on the long-term molsidomine therapy of 6 weeks’ duration. Subsequently, 4 of the seven patients were further placed on very long-term molsidomine therapy of 6 months’ duration. All patients had clinically stable anginal pain associated with ST-segment depression of more than 0.1 mV on exercise. Patients with clinical signs of congestive heart failure or unstable angina were excluded from the study. The purpose of the study was carefully explained to the patients, all of whom gave their consent. The study began more than one week.

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<table>
<thead>
<tr>
<th></th>
<th>placebo (N = 8)</th>
<th>1 day (N = 8)</th>
<th>2 week (N = 8)</th>
<th>6 week (N = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest HR (beat/min)</td>
<td>77 ± 8</td>
<td>82 ± 3</td>
<td>82 ± 5</td>
<td>81 ± 3</td>
</tr>
<tr>
<td>Exercise HR (beat/min)</td>
<td>117 ± 7</td>
<td>124 ± 8</td>
<td>126 ± 8</td>
<td>115 ± 9</td>
</tr>
<tr>
<td>Rest SBP (mmHg)</td>
<td>120 ± 4</td>
<td>100 ± 5***</td>
<td>115 ± 4*</td>
<td>114 ± 3</td>
</tr>
<tr>
<td>Exercise SBP (mmHg)</td>
<td>154 ± 3</td>
<td>135 ± 4**</td>
<td>151 ± 4</td>
<td>154 ± 4</td>
</tr>
<tr>
<td>Rest HR × SBP (× 10^3)</td>
<td>9.0 ± 0.5</td>
<td>8.1 ± 0.4*</td>
<td>9.3 ± 0.4</td>
<td>9.4 ± 0.5</td>
</tr>
<tr>
<td>Exercise HR × SBP (× 10^3)</td>
<td>18.1 ± 1.2</td>
<td>16.8 ± 1.1</td>
<td>18.5 ± 1.5</td>
<td>18.3 ± 1.6</td>
</tr>
<tr>
<td>Exercise duration (min)</td>
<td>11.4 ± 1.7</td>
<td>13.6 ± 1.2***</td>
<td>13.3 ± 1.2*</td>
<td>12.2 ± 1.3#</td>
</tr>
<tr>
<td>Time to ischemia (min)</td>
<td>9.0 ± 1.7</td>
<td>12.8 ± 1.2***</td>
<td>11.8 ± 1.0**</td>
<td>10.5 ± 1.3#</td>
</tr>
<tr>
<td>Exercise stage</td>
<td>4.3 ± 0.6</td>
<td>5.1 ± 0.4**</td>
<td>4.9 ± 0.4*</td>
<td>4.7 ± 0.5</td>
</tr>
<tr>
<td>Treadmill Score</td>
<td>-47 ± 24</td>
<td>1 ± 14*</td>
<td>-8 ± 15</td>
<td>-15 ± 16</td>
</tr>
<tr>
<td>ST-segment deviation at rest (mm)</td>
<td>-0.32 ± 0.14</td>
<td>0.12 ± 0.14</td>
<td>-0.20 ± 0.08</td>
<td>-0.27 ± 0.16</td>
</tr>
<tr>
<td>ST-segment deviation on exercise (mm)</td>
<td>-2.00 ± 0.25</td>
<td>-1.60 ± 0.20***</td>
<td>-2.33 ± 0.30</td>
<td>-2.16 ± 0.28</td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.01, *** p < 0.001 for placebo vs data  # p < 0.05 for 2 weeks vs 6 week's data

later, but not more than one month after the coronary angiographic study, and was performed during admission in three patients (Case 6, 7, 8) and on outpatient basis in the remaining subjects (Case 1, 2, 3, 4, 5).

**Protocol**

Graded exercise testing during the fasting state was performed on a treadmill test using a modified Bruce protocol in which two additional lighter exercise stages were added to the original Bruce protocol. Therefore, the first stage of Bruce protocol is equivalent to the third stage of the modified protocol. A full, 12-lead ECG was recorded on a three-channel recorder (Computer Assisted Stress Electrocardiography (CASE) System, Marquette Electronics Co., Inc., Milwaukee, Wisconsin) with silver/silver-chloride electrodes. The electrodes were carefully placed: two in the infraclavicular areas bilaterally on the manubrium sterni, one just above the left iliac crest and the rest over the standard chest position. During the entire period of the exercise test leads V1, V4 and aVF were recorded continuously from the onset of exercise to the end of recovery (Fig. 1). The exercise was terminated when the patients complained of moderately severe chest pain, exhaustion, shortness of breath or leg fatigue, or when frequent premature ventricular contractions, ventricular tachycardia, hypotension or 3 mm ST-segment depression appeared. Treadmill exercise score was computed to quantitate the severity of ischemia according to Hollenberg’s method: Area of J-point and ST slope curves (V4, aVF) / Duration of exercise x % maximal predicted heart rate. Prior to our scheduled studies, all patients had experienced treadmill test on at least two different days. These preliminary tests were performed to make the patients accustomed to the procedures and to examine the reproducibility of the treadmill test. The treadmill test was performed during the placebo period, on the first day of administration of 2 mg of molsidomine and after 2 weeks of 2 mg tid administration in the acute trial. The test repeated after 6 weeks and after 6 months of molsidomine administration in the long term trial, and three days after cessation of the administration in four patients. All the tests were performed at 90 minutes post-drug ingestion in an air-conditioned room.

Significance of the differences of the results for each patient were analyzed using paired t-test.

**RESULTS**

The hemodynamic changes produced by placebo and molsidomine during exercise are summarized in Table II.

**Heart rate, blood pressure and double products**

During molsidomine treatment, resting heart rate (HR) and exercise HR were not significantly
changed on the first day, at 2 weeks, and at 6 weeks. Resting systolic blood pressure (SBP) decreased from $120 \pm 4$ mmHg on the placebo to $100 \pm 5$ mmHg ($p < 0.001$) on the first day and to $115 \pm 4$ mmHg ($p < 0.05$) after 2 weeks. Exercise SBP was reduced from $154 \pm 3$ to $135 \pm 4$ mmHg ($p < 0.01$) on the first day administration, but did not show any change thereafter. Resting diastolic blood pressure (DBP) and exercise DBP were not significantly reduced, although exercise DBP could not be measured in some patients. The maximal double product (HR $\times$ SBP) at the time of induced angina attack did not differ significantly in the tests performed for the various periods of therapy. A decrease in the resting double product from $9.0 \pm 0.5 \times 10^3$ to $8.1 \pm 0.4 \times 10^3$ ($p < 0.05$) was noted only on the first day.

**Exercise duration and time to ischemia**

The exercise duration required to produce an angina attack was significantly increased from $11.4 \pm 1.7$ to $13.6 \pm 1.2$ min ($p < 0.001$) on the first day of therapy. However, five of the seven patients studied showed a decrease in the exercise duration ($12.2 \pm 1.3$ min) after 6 weeks, when compared to that ($13.3 \pm 1.2$ min) after 2 weeks of therapy ($p < 0.05$) (Fig. 2A). The exercise time up to the onset of ST-segment depression was similarly prolonged during all periods of treatment, although the prolongation after 6 weeks was not significantly different from
that of the placebo period. There was a decrease in the time up to the onset of ischemia after 6 weeks in 5 of the 7 patients when compared with that after 2 weeks of therapy (Fig. 2B).

**ECG changes and treadmill exercise scores**

The ST-segment deviation at rest did not change significantly following molsidomine therapy, when compared with that of the placebo period. However, the ST-segment deviation at the onset of angina was significantly \( p < 0.001 \) decreased on the first day from \( 2.00 \pm 0.25 \) to \( 1.60 \pm 0.20 \) mm. The decrease in the ST-segment deviation was not noted at the other periods of therapy. Treadmill exercise score improved in 7 out of 8 patients through all periods of therapy, although significant improvement took place only on the first day of therapy (Fig. 3). However, the score deteriorated considerably after 6 weeks as compared to that on the first day of therapy \( (1 \pm 14 \text{ to } -15 \pm 16) \).

**The discontinuation of molsidomine therapy after long-term administration**

Four of 8 patients studied were placed on a very long-term therapy for 6 months. In patients 4 and 5, exercise duration at 6 months showed a further decrease, compared with that after 6 weeks. On the third-day after the cessation of therapy there was a slight increase in exercise duration in 3 patients. The time up to the onset of angina was also shortened at 6 months of the therapy, compared with that after two weeks of therapy in two of the patients. The time up to the onset of ischemia in the treadmill test performed after cessation of therapy showed no significant change, although it was increased in one of the patients. Treadmill score was slightly deteriorated following continuous therapy for 6 months in three patients. The discontinuation of molsidomine treatment did not deteriorate the treadmill score in the subjects. One patient showed a paradoxical improvement of his score after cessation of drug administration, although the cause was unknown.

**DISCUSSION**

The present study confirms, as previously reported, that molsidomine can increase exercise tolerance and the time up to the onset of ischemia in patients with typical effort angina. This increase in tolerance appeared to be most manifested on the first day of molsidomine administration and could be maintained for two weeks of therapy. However this tolerance tended to decrease after six months of treatment. There was no deterioration of exercise tolerance and the time up to the onset of ischemia after the discontinuation of 6 months' therapy. Our results indicate that long-term treatment can induce a drug tolerance.

**Reliability of treadmill test**

The reproducibility was examined by performing at least two treadmill tests prior to the drug treatment. Therefore, improvement observed after molsidomine may not be due to the training effect. Moreover, ST-segment deviation and ST-slope were measured on a computer-based algorithm with no subjective deviation. Redwood has suggested appropriate duration of exercise time to cause angina is 3 to 6 min, which was found to be highly reproducible. This is true in the bicycle ergometer. Even if exercise duration was over 6 min on the treadmill test, a highly reproducible exercise duration could be obtained in our laboratory, as shown in Fig. 4. There was a significant difference \( (p < 0.05) \) in the exercise duration between the first and second treadmill test. However, no further prolongation of the exercise duration was noted in the third treadmill test.

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test. The modified Bruce protocol used in this study adds two stages of lighter exercise to the original Bruce protocol. The conventional program such as the Bruce protocol could not be tolerated for even the first stage of exercise by two patients in our study.

The action of molsidomine
Molsidomine, a recently synthesized syndenomine derivative, is playing an important role in the treatment of angina and congestive heart failure. The action of molsidomine to relieve angina is similar to that of the nitrates, but the effects last longer.10,18 The action persisted for 5 hours while that of isosorbide dinitrate was observed for only 45 min. Tanayama reported that molsidomine was gradually metabolized in the liver to 3-morpholinosydnonimine which was non-enzymatically changed to N-cyanomethylene aminomorpholine.19 The long-lasting effects of molsidomine may be explained by the anti-anginal action of its metabolites such as 3-morpholinosydnonimine (SIN-1) and N-nitroso-N-morpholino-acetonitrile (SIN-1A). SIN-1A is said to possess a hypotensive action comparable to that of nitroglycerin and SIN-1, which has a hypotensive action somewhere inbetween molsidomine and SIN-1A. In contrast, nitroglycerin is metabolized in the liver to non-active form. It has been shown that molsidomine is an effective antianginal agent during a short period of administration. Takeshita11 has shown that it increases exercise tolerance to the same extent as nitroglycerin two hours after a single oral administration. Röhl12 reported that the effect of molsidomine on exercise tolerance already appeared after 30 min and continued until 6 hours after the sublingual administration.

Documentation of chronic molsidomine efficacy in angina pectoris
No report has been made regarding the effects of long-term administration of molsidomine and its drug tolerance. Our study has shown that both the exercise duration and the time up to the onset of ischemia are most markedly increased on the first day, but began to decrease significantly after six weeks of molsidomine treatment. The greatest increase in exercise duration on the first day is associated with a decrease in ST-segment deviation at submaximal exercise, systolic blood pressure, and treadmill score. After two weeks of therapy, the exercise duration remained significantly increased despite the absence of a decrease in ST-segment deviation on submaximal exercise. The absence of a decrease in ST-segment deviation indicates that patients performed a submaximal exercise until ischemia occurred to the same extent as in placebo period. There was a significant decrease in the efficacy of molsidomine in the sixth week of administration which may be explained partly by drug tolerance. There is further evidence of drug tolerance in that a treadmill test done three days after discontinuation of the therapy did not show any deterioration of the exercise duration and the time up to the onset of ischemia. However the number of cases in this study is limited, so further study is necessary to reach a final conclusion. Although there has been no report about drug tolerance of molsidomine, nitroglycerin was reported to attain drug tolerance within two weeks.17

Mechanism of action of Molsidomine
After administration of molsidomine the exercise capacity of our patients was increased without being accompanied by an increase in the double product. This finding may imply that the cardiac oxygen consumption at post-drug was decreased at the same level of exercise as at pre-drug. The decrease in cardiac oxygen consumption appeared to be mainly due to the decrease in the preload of left ventricle which was induced by decreased venous tone and venous return.18 Grund reported that the systemic venous capacitance was increased in a heart-lung bypassed dog by 1 mg/kg of the intravenous administration of molsidomine.5 Fiedler and Shoitholt also demonstrated a decrease in the left ventricular enddiastolic pressure after intravenous administration in the dog.20 In man, Aptecar observed a decrease in pulmonary artery pressure and pulmonary wedge pressure, using Swan-Ganz catheter in patients with acute myocardial infarction.10 There was also a reduction in the enddiastolic pressure and volume reduction in man after intravenous injection of molsidomine in patients with coronary artery disease.9 A direct calculation of myocardial oxygen consumption was performed in the dog and in man, with a decrease of approximately 24%.6 Detry maintains that the principal mechanism of action may be due to a decrease in afterload.21 From the standpoint of coronary circulation the decrease in the afterload may lead to the impairment in the myocardial ischemia.22-24 However, the afterload reduction results in the decrease in the preload in the in
situ heart, which improves the subendocardial blood flow in the ischemic myocardium.\textsuperscript{25} Molsidomine was reported to improve the blood flow in the ischemic region\textsuperscript{26} In our study the significant decrease in systolic blood pressure was found only on the first day of administration, with a maximal increase in the exercise duration and the time up to the onset of ischemia. After two weeks and after 6 weeks of therapy there was no decrease in blood pressure, but there was still an increase in the exercise duration. Therefore both preload and afterload reduction were effective at the early phase of administration. Only preload reduction is responsible for improvement of ischemia during the chronic stage of administration, which results in a decrease in the efficacy of this drug.

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