Increased Exercise Tolerance After Nitroglycerin Oral Spray: A New and Effective Therapeutic Modality in Angina Pectoris

Asher Kimchi, M.D., Garrett Lee, M.D., Ezra Amsterdam, M.D., Ken Fujii, B.S., Paul Krieg, B.S., and Dean T. Mason, M.D.

SUMMARY The prophylactic antianginal efficacy of nitroglycerin (NTG) oral spray was assessed in 20 patients with angiographically documented coronary disease and stable angina pectoris. The evaluation was by a randomized crossover trial involving treadmill exercise testing. On study day 1, a control treadmill exercise test was performed, followed 30 minutes later by a second exercise test 2 minutes after administration of either placebo (group A, 10 patients) or NTG spray 0.8 mg (group B, 10 patients). One week later, on study day 2, the patients again underwent control treadmill exercise testing followed by a second exercise test after either NTG spray (group A) or placebo (group B). NTG spray delayed the onset of anginal pain during exercise by a mean of 100 ± 64 seconds (p < 0.001) in 13 patients and prevented pain entirely in seven. Placebo did not significantly delay the appearance of angina and prevented chest pain in only one patient. NTG spray increased treadmill exercise duration by 31% before the onset of angina (p < 0.001); placebo did not significantly alter the duration of exercise. NTG spray abolished in six patients and delayed in 14 patients the onset of exercise-induced ST-segment depression of 1 mm (p < 0.001). Patients achieved a higher heart rate at peak exercise with NTG spray, and yet the maximal exercise-induced ST-segment depression of 2.1 ± 1.0 mm during the control study declined to 1.3 ± 0.9 mm on NTG spray (p < 0.001). Placebo had no effect on exercise ST-segment depression. These data indicate that the oral NTG spray is an effective prophylactic for exercise-induced angina.

THE MAINSTAY of treatment for angina pectoris for the last hundred years has been nitroglycerin (NTG). 1 NTG reliably relieves angina and augments exertional tolerance when used prophylactically. 2-5 When administered sublingually in tablet, NTG reaches peak blood levels 2 minutes after its dissolution. 7 However, the time required for the tablet to dissolve varies from person to person and further delays the onset of action for pain relief. NTG oral spray theoretically should eliminate the time required for tablet dissolution. When sprayed onto the tongue, it is directly absorbed and thus might afford more rapid and reliable action.

We assessed the therapeutic efficacy of NTG spray in patients with exercise-induced angina and obtained subjective and objective measurements during treadmill exercise testing. Our initial experience with NTG spray has been presented in preliminary form. 8

Methods

Patients

Twenty patients (17 males and three females), mean age 61 years (range 50–74 years), with stable, exercise-induced angina pectoris participated in this trial. Their history of angina ranged from 6 months to 12 years (average 44 months). All patients had angiographically demonstrable coronary artery disease, and had at least 70% narrowing of luminal diameter in at least one major coronary artery. Ten patients had had a myocardial infarction at least 6 months before the study. Five patients had undergone coronary artery bypass graft surgery but continued to have stable angina. None of the patients were hypertensive or had clinical or radiologic evidence of heart failure. All patients had undergone treadmill exercise testing within 6 months before the study; treadmill exercise-induced angina and ischemic ST depression of 1.0 mm or more lasting at least 0.08 second occurred in each patient. All patients tolerated a 0.8-mg dose of sublingual...
gual NTG with no or minimal side effects. All cardiac medications except sublingual NTG were discontinued 24 hours before the study; sublingual NTG, food and cigarettes were withheld for 4 hours before the study. Informed, written consent was obtained from all patients. The protocol was approved by our institutional Human Subjects Review Committee.

NTG Spray  
NTG oral spray (Nitrolingual) — glyceryl trinitrate in aromatized oily solution — is enclosed in an aerosol container that holds 10 ml of solution, enough for about 200 doses of 0.4 mg NTG each. The drug is administered onto the oral mucosa — preferably the tongue — without inhaling. During application, the spray is kept vertical with the nozzle head pointing upward and as close to the mouth as possible. Each spray lasts about 200 msec.

Study Design  
Exercise testing was performed according to the Bruce protocol. A single-blind design was used. Patients were randomized into two groups of 10 patients each. On day 1 of the study, both groups underwent a control exercise test, followed 30 minutes later by a second exercise test, which was performed 2 minutes after two squirts of placebo (group A) or two squirts of NTG, 0.8 mg (group B) were sprayed onto the tongue (table 1). Day 2 of the study was conducted an average of 7 ± 2 days later. Patients again underwent a control treadmill exercise test followed by a second exercise test 30 minutes later, after either NTG spray or placebo. Thus, the single-blind study design provided for assessment of two randomized, parallel groups that received placebo and NTG spray in reverse order. The patients were instructed to indicate the onset of angina, the onset of moderate to moderately severe chest pain* necessitating discontinuation of exercise, and the time at which chest pain completely subsided after exercise. Electrocardiographic leads 1, aVF, and V₅ were constantly monitored on an oscilloscope and a 12-lead ECG was recorded every minute during exercise, at the onset of angina, at the termination of exercise and every minute during the recovery period. The end point of exercise was moderate (2+) or moderately severe (3+) chest pain. Precautions were taken to control the factors that could produce changes in exercise tolerance. The laboratory temperature was kept at 20–24°C, and the patient was familiarized with the protocol and the staff to reduce apprehension.

Measurements and Recordings  
Heart rate and blood pressure were measured in the sitting and standing positions before the drug treatment, and 1 (sitting position) and 2 minutes (standing) after NTG or placebo. Blood pressure was measured by cuff sphygmomanometry. Other measurements included time of onset of angina and appearance of 1.0 mm of ST-segment depression lasting at least 0.08 second, maximal duration of exercise, maximal estimated total body oxygen consumption (VO₂), maximal values for exercise heart rate, blood pressure, double product of heart rate and systolic blood pressure, ST-segment depression and severity of chest pain (0–4 + scale) at peak exercise.

Statistical Analysis  
The paired t test was used for statistical analysis. The significance of the difference in the time of onset of 1 mm of ST-segment depression was determined by the Wilcoxon paired signed-rank test. For all variables measured, the difference between NTG and placebo with respect to their control tests was determined. Values are given as mean ± SD; p < 0.05 was considered significant.

Results

Hemodynamic Data Before Exercise (table 2)  
In the sitting position 1 minute after NTG spray, there was no significant change in heart rate compared with control. However, 2 minutes after administration of NTG spray in the standing position, mean heart rate increased significantly (p < 0.01). Placebo spray did not increase heart rate either in the sitting or standing position. Systolic blood pressure declined significantly after NTG spray in the sitting and standing positions (p < 0.001). Placebo spray had no significant effect on systolic blood pressure in the standing position.

Effect on Exercise-induced Angina and Exercise Tolerance  
NTG spray relieved symptoms in all 20 patients. The onset of angina was delayed by a mean of 100 ± 64 seconds (p < 0.001) in 13 patients and pain was totally prevented in seven patients. Placebo delayed the onset of angina in 11 patients, but the magnitude of the delay was not significant (17 ± 39 seconds); placebo prevented angina in only one patient.

Exercise tolerance as assessed by maximal exercise duration improved significantly after NTG. NTG spray extended exercise duration 31%, from 321 ± 97 to 420 ± 111 seconds (p < 0.001). In contrast, there was no significant alteration after placebo compared with control (300 ± 97 vs 312 ± 97 seconds).

Estimated maximal total body oxygen consumption (VO₂ max) at peak exercise increased from 24.1 ± 3.8 to 27.6 ± 4.9 ml/kg/min (p < 0.001) after NTG spray, but did not significantly change after placebo (22.9 ± 3.7 to 23.4 ± 3.8 ml/kg/min).

Hemodynamic Data at Maximal Exercise  
Maximal heart rate increased in all patients after

<table>
<thead>
<tr>
<th>TABLE 1. Treadmill Test Study Design</th>
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<tbody>
<tr>
<td><strong>Day 1</strong></td>
</tr>
<tr>
<td><strong>(n = 10)</strong></td>
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<tr>
<td>2. After placebo</td>
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<tr>
<td><strong>Day 2</strong></td>
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<tr>
<td>(1 week later)</td>
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*Chest pain scale: 0 = no pain; 1+ = mild pain; 2+ = moderate pain; 3+ = moderately severe pain (or equivalent to that which usually necessitated discontinuation of activity); 4+ = very severe pain equivalent to the most severe pain the patient had experienced.
Table 2. Preexercise Hemodynamic Results

<table>
<thead>
<tr>
<th></th>
<th>Nitroglycerin spray</th>
<th>Placebo spray</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting</td>
<td>64 ± 11</td>
<td>65 ± 12</td>
</tr>
<tr>
<td>Standing</td>
<td>70 ± 13</td>
<td>76 ± 16</td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
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<tr>
<td>Sitting</td>
<td>124 ± 15</td>
<td>117 ± 14</td>
</tr>
<tr>
<td>Standing</td>
<td>120 ± 14</td>
<td>113 ± 15</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

Measurements in the sitting position were taken 1 minute after administration of nitroglycerin or placebo. Measurements in the standing position were taken 2 minutes after administration of nitroglycerin or placebo.

NTG spray. The mean increase was 12% (122 ± 19 to 137 ± 19 beats/min, p < 0.001), whereas there was no difference after placebo (118 ± 19 vs 120 ± 21 beats/min).

Maximal exercise double product increased after NTG spray (23.2 ± 3.7 × 10^3 vs 20.7 ± 3.6 × 10^3, p < 0.01). There was no significant change in double product after placebo spray.

ST-segment Depression at Maximal Exercise

During control exercise testing, all patients had at least 1 mm of ST-segment depression. NTG spray delayed the onset of 1 mm of ST depression in 14 patients. On the average, ST-segment depression appeared between the third and fourth minutes of control exercise (mean 3.6 ± 1.3 minutes, median 3.7 minutes) and between the fifth and sixth minutes (mean 5.6 ± 1.8 minutes, median 6.1 minutes) of exercise after NTG spray (p < 0.001). In the remaining six patients, ST-segment depression was totally abolished after NTG spray. Placebo did not significantly delay or prevent ST-segment depression.

Maximal exercise-induced ST-segment depression was reduced significantly after NTG spray (2.1 ± 1.0 to 1.3 ± 0.9 mm, p < 0.001) despite a higher work load in the NTG-treated group. Placebo had no effect on ST-segment depression at peak exercise (2.0 ± 0.9 [placebo] and 1.9 ± 0.9 mm [control]).

Adverse Side Effects

Only three patients complained of headaches after NTG spray. All 20 patients completed the study without experiencing major adverse side effects.

Discussion

This study demonstrates the prophylactic antianginal efficacy of NTG oral spray in patients with documented coronary artery disease and exercise-induced angina pectoris. This new mode of NTG application significantly increased treadmill exercise duration and work load before the onset of angina compared with placebo spray. The magnitude of improvement in exercise duration (31%) in our patients is consistent with the beneficial effect of sublingual NTG demonstrated by others.2-6 The reduction of blood pressure in both the sitting and standing positions and elevation of heart rate in the standing position parallel the characteristic hemodynamic changes observed after sublingual NTG, indicating absorption and pharmacologic activity of the drug in the spray form. The hemodynamic effects were rapid in onset (less than 2 minutes).

Previous studies have indicated that the antianginal action of NTG derives principally from reduction of myocardial oxygen demand through diminution of myocardial wall tension.4, 11, 12 This effect results from the peripheral arteriolar and venous dilating actions of the drug, which reduce systolic blood pressure and ventricular volume, the major determinants of myocardial wall tension.4, 13, 14 Alleviation of myocardial ischemia and angina results from improvement in the relationship between myocardial oxygen supply and demand after reduction in the latter. A favorable effect on the distribution of myocardial blood flow after NTG has also been suggested, but reduction of cardiac oxygen demand appears to be the principal antianginal mechanism of the drug.4, 15

The oral spray is a new and effective modality of achieving the effects of NTG. In theory, the NTG spray affords greater stability than sublingual tablets because the spray is a lipid solution in a metal container and is administered by metered dose. In contrast, repeated opening of a bottle of sublingual NTG tablets can accelerate chemical breakdown of glyceryl trinitrate to less active compounds by exposure to atmospheric heat, light and moisture. Further, administration of NTG oral spray is safe. No adverse effect was experienced by patients receiving NTG oral spray in this investigation.

The encouraging results of our single-blind, randomized, crossover study warrant double-blind analysis of oral NTG spray in a larger number of patients.

Acknowledgment

We are grateful to G. Pohl Boskamp Pharmaceutical Laboratories, Hohenlockstedt, West Germany, for supplying Nitrolingual spray and identical placebo. We are indebted to Morray Bear, M.A., for help with the statistical analyses, to Becky Kimchi, Alice Feldman, Hattie Ellingburg, Patricia Weathers and Libby Sterling for their assistance and to Alan Rozanski, M.D., for his advice concerning this manuscript.

References

Total Cholesterol and Lipoproteins in School Children: Prediction of Coronary Heart Disease in Adult Relatives

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HYMIE GORDON, M.D., RALPH D. ELLEFSON, PH.D., PATRICIA A. HODGSON, M.S.,
AND BRUCE A. KOTTKE, M.D.

SUMMARY The distribution of risk factors and the prevalence of coronary heart disease (CHD) were studied in 850 first- and second-degree relatives of 98 healthy index cases selected from 3666 school children surveyed for lipid levels in Rochester, Minnesota. Three groups of families were based on an index child’s total plasma cholesterol level: 18 families with a child in less than the fifth percentile (low-cholesterol group), 47 with a child in the fifth to ninety-fifth percentiles (middle-cholesterol group) and 33 with a child in greater than the ninety-fifth percentile (high-cholesterol group). The children’s cholesterol levels clustered with those of their relatives; mortality due to CHD before age 65 was increased by 2.5 times in grandfathers of index cases in the high-cholesterol group compared with those of the middle-cholesterol group (p < 0.016). The prevalence of CHD in all the grandfathers was associated with an index child’s total cholesterol, more strongly associated with an index child’s low-density lipoprotein cholesterol level and most strongly associated with an index child’s high-density lipoprotein cholesterol level as a fraction of total cholesterol. This study establishes that childhood lipid and lipoprotein levels from a single cross-sectional survey identify families at elevated risk for CHD.

ATHEROSCLEROSIS underlies most coronary heart disease (CHD), but is difficult to study because a large proportion of the population with affected arteries has no easily detected manifestation of the disease. As a consequence, much of the emphasis in studies of CHD has been on the analysis of factors thought to be pathogenic. Goldstein et al. reported lipid abnormalities in 60% of a sample of men younger than 40 years of age and women younger than 50 years of age with myocardial infarction (MI). Heterozygous parents of children with one type of familial hypercholesterolemia have early onset of CHD while children who are homozygous often suffer a fatal MI before age 20 years. In a community-wide study, the rate of a first major coronary event in white adult males during a 10-year follow-up increased uniformly with an increase in initial cholesterol levels. Both the low-density lipoprotein (LDL) and high-density lipoprotein (HDL) fractions of serum cholesterol are stronger predictors of CHD in men older than age 50 years than is total cholesterol. Although an elevated LDL level appears to be atherogenic, an elevated HDL level may be antiatherogenic.

Studies in children have provided frequency distributions of lipids and lipoproteins by age and sex and evidence that a person’s cholesterol levels measured

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