Sustained Hemodynamic and Antianginal Effect of High Dose Oral Isosorbide Dinitrate

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SUMMARY Twenty-one patients with documented coronary atherosclerotic heart disease were studied to determine the effect of high dose oral isosorbide dinitrate (ISDN) on heart rate, blood pressure, and exercise time until angina pectoris. Patients were tested in two phases, initially with 0.4 mg of sublingual nitroglycerin and with sublingual placebo, and then with oral ISDN, mean dose 29 mg, and oral placebo. Both phases of the study were conducted in a randomized, double-blind, crossover manner. After ISDN was compared to oral placebo, heart rate increased at 30 to 300 min (P < 0.01) (peak increase 18 beats/min at 60 min), and systolic blood pressure decreased from 45 to 300 min (P < 0.005) (peak decrease 18 mm Hg at 60 min). Exercise time at 2 min after sublingual nitroglycerin increased 51% as compared to sublingual placebo (P < 0.001). After ISDN was compared to oral placebo, exercise time increased 54% at 1 hr (P < 0.005), 37% at 3 hr (P < 0.01), and 12% at 5 hr (NS). Twelve of 21 patients (57%) improved their exercise time until angina ≤ 25% at 1 hr after oral ISDN. The exercise response to sublingual nitroglycerin was a good predictor of this response to oral ISDN.

SUBLINGUAL NITROGLYCERIN has enjoyed longstanding and almost universal acceptance as an antianginal agent. The remarkable efficacy of this drug has led to its use not only as a therapeutic agent but also as a standard for evaluating other antianginal agents and even as a diagnostic tool. Many attempts have been made to prolong the brief action of sublingual nitroglycerin by altering both molecular structure and method of administration. These attempts have generated a long history of controversy, still unresolved. Orally administered nitrates in particular have been subject to attack. Needleman and associates working with rats, reported rapid and nearly complete degradation by the liver of orally administered nitrates. Thus it has been argued that there is no rational basis for the use of orally administered nitrates.

More recent hemodynamic studies, however, have caused us to reexamine this issue. Decreases in arterial blood pressure and left ventricular filling pressure following oral isosorbide dinitrate (ISDN) have been demonstrated in several carefully conducted studies in cardiac patients. These hemodynamic effects suggested that an antianginal effect might also be present. Careful review of previous studies on the antianginal effect of oral isosorbide dinitrate


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suggested that inadequate dosage may have prevented the demonstration of antianginal efficacy. 17, 18

Our study was designed to answer the following questions. Can hemodynamic effects from large, individually determined doses of oral ISDN be demonstrated in patients with angina pectoris due to coronary heart disease but without congestive heart failure? Can antianginal efficacy be demonstrated? What is the relationship between the response to sublingual nitroglycerin and the response to oral ISDN?

Methods

Twenty-one men between 42 and 64 years of age with documented coronary atherosclerotic heart disease and typical effort angina pectoris were studied. Twenty patients had either a history of a clearly documented myocardial infarction and/or coronary angiographic demonstration of greater than 70% luminal narrowing in at least one major coronary artery. One patient (patient 12) gave a history of myocardial infarction which was not documented. One mm flat ST-segment depression developed with typical angnal pain during exercise electrocardiography in this patient. All patients signed consent forms approved by the hospital Human Studies Subcommittee.

All patients reported benefit from sublingual nitroglycerin for relief or prevention of angina pectoris. The presence of any of the following excluded patients from the study: myocardial infarction or onset or significant change in angina pectoris within the previous 6 months; history, physical findings, or a liver function abnormality (serum glutamic oxiadecit transaminase, bilirubin, albumin, or total protein) consistent with liver disease; a blood pressure $\geq 150/100$ mm Hg; or history, physical findings, or chest roentgenographic evidence of congestive heart failure. Nocturnal angina without evidence of congestive heart failure was not an excluding factor.

A history of nocturnal angina on at least one occasion could be elicited from eight study patients. Two of these eight patients were receiving digoxin therapy, initiated because of nocturnal angina. The digoxin therapy had produced no change in symptoms when it had been initiated and no change occurred when the digoxin was stopped one week prior to the study.

Propranolol therapy was gradually tapered prior to the study. No patient received propranolol, digitalis, or diuretics during or for 72 hours prior to the study period. Nitrates were given only as prescribed by the study protocol, and no other vasodilators were received during or for 72 hours prior to the study period.

Patients were hospitalized for five days for this study. Practice exercise tests were performed on the first two hospital days. All patients had at least two practice exercise tests prior to definitive testing. Exercise testing was performed in a sitting position on a Collins* constant load bicycle ergometer. The workload was increased by 25 watt increments every 3 min. The initial workload was chosen so that angina pectoris developed between 3 and 6 min during control testing. Four patients had control exercise times of less than 3 min despite an initial workload of only 25 watts. Patients were exercised to the onset of angina pectoris or, if angina did not occur, to exhaustion. Exercise times were measured to the onset of angina but patients continued to exercise until blood pressure could be measured and an electrocardiographic strip recorded.

Simultaneous electrocardiographic leads II and V1 were recorded via telemetry in the supine and sitting positions before exercise and in the sitting position during exercise, at the end of exercise, 30 sec after exercise, 1 min after exercise, and at 1 min intervals for at least 1 to 6 min after exercise. Heart rates were measured from the electrocardiograms. Blood pressures were recorded using a mercury sphygmomanometer with the patient in the supine and sitting positions before exercise and in the sitting position at the end of exercise.

Test doses of oral ISDN were administered on hospital days 1 to 3, but none were given for at least 16 hours prior to exercise testing. Isosorbide dinitrate dosage was individually determined by side effects and by the response of heart rate and blood pressure in the sitting position from 1 to 3 hours after administration. An attempt was made to maximize ISDN dosage while avoiding significant headache or a precipitous fall in blood pressure. All patients had at least a 10 mm fall in systolic blood pressure and/or a 10 beat/min increase in heart rate following the chosen dose of ISDN during this dose selection phase.

On the third through fifth hospital days, definitive exercise testing was performed. On each of these three days, patients were brought to the exercise laboratory in a fasting state at 8 A.M. Fasting was continued for the duration of each day’s testing. No smoking was allowed during or for eight hours prior to each day’s testing.

On the third hospital day, patients received two exercise tests with two hour separations between the tests. Sublingual nitroglycerin 0.4 mg and sublingual placebo of identical appearance were given 2 min prior to the beginning of exercise in a double-blind, randomized, crossover manner. Blood pressure and heart rate were determined in the sitting position immediately prior to drug administration and 2 min later, immediately prior to exercise. Patients 1 through 4 were tested with sublingual nitroglycerin and with sublingual placebo approximately 2 to 3 months after they were tested with oral ISDN.

On the fourth and fifth hospital days, patients received a control exercise test followed in 15 min by oral drug administration and then exercise tests at 1, 3, and 5 hours after drug administration. Patients received oral ISDN and oral placebo of identical appearance in a randomized, double-blind, crossover manner.† In addition to blood pressure and heart rate determinations prior to and during each exercise test, blood pressures and heart rates were measured in a sitting position at 15, 30, 45, 90, 120, 150, 240, and 270 min after oral drug administration.

The data were analyzed by our biostatistician with a computer using Student’s $t$-test for correlated means to determine significance levels. Correlation coefficients were calculated using Pearson’s product moment method.

*Warren E. Collins, Inc.

†Oral ISDN and oral placebo of identical appearance were supplied through Dr. Clarence Denton, Ives Laboratories, New York, New York.
TABLE 1. Clinical Data

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Abbreviations: Prev MI = previous myocardial infarction; P = propranolol; Noct ang = nocturnal angina; CABG = coronary artery bypass graft surgery; N = any nitrate other than sublingual nitroglycerin in the month prior to study; ISDN = oral isosorbide dinitrate.

Results

Table 1 provides the clinical data and the ISDN dosage used in the study. The mean dose of ISDN was 29 mg with a range from 20 to 50 mg.

Exercise times for each patient after sublingual nitroglycerin and sublingual placebo, at 1, 3, and 5 hours after oral placebo and its control period, and at 1, 3, and 5 hours after oral ISDN and its control period as well as the mean exercise times are shown in table 2.

Compared to sublingual placebo, the mean exercise time increased 106 sec after sublingual nitroglycerin (P < 0.001). Compared to a control mean of 253 sec, the mean exercise time after oral ISDN increased to 399 sec at 1 hour (P < 0.001), to 347 sec at 3 hours (P < 0.001), and to 290 sec at 5 hours (NS). The mean control exercise time for oral placebo was 226 sec with increases to 255 sec at 1 hour (P < 0.02), 247 sec at 3 hours (NS), and 235 sec at 5 hours (NS).

In order to correct for the placebo effect, the change in exercise time after ISDN (ISDN exercise time minus control exercise time) was compared to the change following oral placebo (placebo exercise time minus control exercise time). Using this method, there was a mean net increase in exercise time after ISDN of 118 sec at 1 hour (P < 0.005), 74 sec at 3 hours (P < 0.01), and 28 sec at 5 hours (NS).

The data were also analyzed by calculating a percentage change after sublingual nitroglycerin and a percentage net change after ISDN, as defined in table 3. The mean percentage change after sublingual nitroglycerin was +51%. The mean percentage net change after ISDN was +54% at 1 hour, +36% at 3 hours, and +13% at 5 hours.

There was no significant difference in control measurements prior to ISDN as compared to control measurements prior to placebo for any parameter measured in this study. In view of the multiple exercise tests required by our protocol, a training or order effect was looked for. The control exercise times on day 4 (first day of ISDN and oral placebo testing) were compared to the control exercise times on day 5 (second day of ISDN and oral placebo testing). The mean exercise times were not significantly different (238 vs 241 sec).

When the exercise times are analyzed for each individual patient, it becomes clear that mean increases after ISDN obscure a wide range of individual responses. As seen in table 3, percentage net changes after ISDN range from...
Nitroglycerin at the other time exercise showed a significant difference after TNG. Six of the control exercise tests and all of the exercise tests after oral and sublingual placebo ended with angina. One patient exercised to exhaustion without developing angina after nitroglycerin. When patients exercised to angina, the intensity and duration of their anginal discomfort was essentially constant for each patient for all tests.

The depth of the ST-segment response to exercise and the duration of ST-segment depression after exercise were also constant for the majority of patients, regardless of changes in the exercise time required to reach an anginal endpoint. None of the 21 patients showed a worsening of the ST-segment response after either ISDN or nitroglycerin. Five of 21 patients (24%) (7, 9, 12, 18, and 19) had \( \geq 1 \) mm less ST-segment depression after exercise following sublingual nitroglycerin. Five of 21 patients (24%) (7, 9, 12, 16, and 18) had \( \geq 1 \) mm less ST-segment depression in response to exercise at 1 hour after ISDN. In all of these five patients, the improvement in ST-segment depression after ISDN persisted for 3 hours, and in two of these five patients, the improvement persisted through 5 hours. Three of the five patients who showed less ST-segment depression after ISDN were patients who exercised to exhaustion without developing angina.

The mean changes in resting heart rate and systolic blood pressure in the sitting position and their statistical significance are graphically displayed in figures 1 and 2. The heart rate increased significantly from 15 min through 300 min with a peak net increase ([ISDN heart rate minus control heart rate] minus [placebo heart rate minus control heart rate]) of 18 beats/min at 60 min after drug adminis-

### Table 3. Percentage Change in Exercise Time after Sublingual Nitroglycerin and Percentage Net Change in Exercise Time after Oral Isosorbide Dinitrate

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<tr>
<th>Pt.</th>
<th>% change after TNG</th>
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<th>% net change 3 hr after ISDN</th>
<th>% net change 6 hr after ISDN</th>
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**Abbreviations:** TNG = sublingual nitroglycerin; ISDN = oral isosorbide dinitrate; ET = exercise time.

\[
\% \text{ change after TNG} = \frac{(\text{TNG ET} - \text{placebo ET}) \times 100}{\text{placebo ET}}
\]

\[
\% \text{ net change after ISDN} = \frac{(\text{ISDN ET} - \text{control ET}) \times 100}{\text{control ET}}
\]

+317% to -87%. Comparison of the 12 patients who showed a 25% or greater net improvement in exercise time at 1 hour after ISDN with the other nine patients revealed no significant difference in age, prevalence of previous myocardial infarction, medications used prior to the study, ISDN dose used during the study, control exercise time, or control exercise time initial workload.

Eleven of 21 patients (52%) increased their exercise time \( \geq 25\% \) after both sublingual nitroglycerin and oral ISDN. Six of 21 patients (29%) failed to increase their exercise time \( \geq 25\% \) after both sublingual nitroglycerin and oral ISDN.
tion. Systolic blood pressure decreased significantly from 30 min through 300 min with a peak net decrease of 18 mm Hg at 60 min. Diastolic blood pressure decreased significantly from 90 min through 270 min with a peak net decrease of 8 mm Hg at 180 min. Heart rate and blood pressure recorded in the supine position showed similar changes but were of less magnitude than those found in the sitting position.

The mean net increase in resting heart rate, measured 2 min after nitroglycerin, was 11 beats/min (P < 0.001). The mean net decrease in systolic blood pressure after nitroglycerin was 11 mm Hg (P < 0.001).

Table 4 shows the mean values for heart rate, systolic and diastolic blood pressure, and product of systolic blood pressure times heart rate at the end of exercise after sublingual placebo and sublingual nitroglycerin, at 1, 3, and 5 hours after oral placebo and its control period, and 1, 3, and 5 hours after oral ISDN and its control period.

The mean heart rate at the end of exercise was 13 beats/min greater after sublingual nitroglycerin than after sublingual placebo (P < 0.001). The mean heart rate at the end of exercise had a net increase of 12 beats/min at 1 hour after ISDN (P < 0.001), a net increase of 5 beats/min at 3 hours after ISDN (P < 0.001), and a net increase of 5 beats/min at 5 hours after ISDN (P < 0.005). Neither oral ISDN nor sublingual nitroglycerin produced a significant change in the mean systolic blood pressure at the end of exercise.

The mean product of systolic blood pressure times heart rate/100 at the end of exercise increased by 21 after sublingual nitroglycerin compared to after sublingual placebo (P < 0.001). The mean product of systolic blood pressure times heart rate/100 at the end of exercise had a net increase of 23.5 at 1 hour after ISDN (P < 0.005), a net increase of 10 at 3 hours after ISDN (P < 0.05), and a net increase of 6.9 at 5 hours after ISDN (NS).

Comparison of the subgroups of patients with and without nocturnal angina revealed no significant difference in exercise times or in heart rate and blood pressure data.

Analysis of the heart rate and blood pressure data for the subgroup of patients with a good response to ISDN (≥ 25% net increase in exercise time at 1 hour) and the subgroup with a poor response to ISDN (< 25% net increase in exercise time at 1 hour) showed significant changes in both subgroups.

### Discussion

Figures 1 and 2 illustrate that a consistent and prolonged hemodynamic response to large oral doses of ISDN was demonstrated in this study. The peak effect on both heart rate and systolic blood pressure occurred at 1 hour after ISDN but significant changes were noted from 15 min through the termination of the study at 5 hours. Franciosa and associates have recently established that hemodynamic effects occur after oral ISDN in patients with congestive heart failure. The question has been raised whether a similar hemodynamic effect will also occur in patients without heart failure, patients in whom the hepatic metabolism of orally administered nitrates may be more efficient. Recent reports by Willis and associates, Kaspar and co-workers, and Poliner and associates indicate that hemodynamic effects do occur following oral ISDN in patients with normal hepatic function and without heart failure. The results reported here further confirm this fact.

The studies of Needleman and associates have frequently been quoted as proving the futility of administering nitrates orally. Needleman's studies were performed in rats and the conclusions were based on an inability to demonstrate a vasodepressor response to nitrates administered orally or directly into the portal vein. Since an unequivocal hemodynamic response to oral ISDN has now been demonstrated in patients both with and without congestive heart failure, Needleman's data would no longer appear relevant to considerations regarding patients. Needleman's studies as well as other studies do suggest that the active vasodilating compound or compounds must be a metabolite of ISDN rather than ISDN itself.

The heart rate and product of systolic blood pressure times heart rate at the end of exercise increased both after nitroglycerin and after ISDN. These findings following nitroglycerin are consistent with the reports of Goldstein and associates, Detry and Bruce, and Robinson. Clausen and Trap-Jensen also showed an increase in product of systolic blood pressure times heart rate at angina after nitroglycerin but the increase was not statistically significant.

The product of systolic blood pressure times heart rate has been used as an index of myocardial oxygen demand but it is both an indirect and incomplete index. Nitrates are known to alter both left ventricular ejection time and left ventricular volume both of which influence myocardial

### Table 4. Mean Heart Rate, Systolic and Diastolic Blood Pressure, and Product of Systolic Blood Pressure Times Heart Rate at End of Exercise after Sublingual Placebo, Sublingual Nitroglycerin, Oral Placebo and Its Control, and Isosorbide Dinitrate and Its Control

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<th>SL TNG</th>
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<td>HR (beats/min)</td>
<td>118</td>
<td>131*</td>
<td>117</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>169</td>
<td>168</td>
<td>139</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>95</td>
<td>94</td>
<td>92</td>
</tr>
<tr>
<td>SBP × HR</td>
<td>199</td>
<td>220*</td>
<td>185</td>
</tr>
</tbody>
</table>

*P < 0.001.
†P < 0.01.
‡P < 0.05.

Sublingual nitroglycerin is compared to sublingual placebo; oral placebo values and oral isosorbide dinitrate values are compared to their respective controls.

Abbreviations: SL = sublingual; TNG = nitroglycerin; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; SBP × HR = product of systolic blood pressure times heart rate/100.
oxygen consumption. Since neither of these parameters, nor many others, were measured in this study, no conclusions can be drawn about how nitrates are changing the myocardial oxygen supply and demand equation.

The exercise times in this study clearly establish the acute antianginal efficacy of oral ISDN when used in high doses. The peak effect occurred at 1 hour with a significant improvement in exercise time persisting through 3 hours in most patients who responded, and, persisting through 5 hours in some patients. A number of previous studies using oral ISDN as an antianginal agent failed to show a beneficial effect. The large, individualized doses of ISDN employed in this study are likely a major factor accounting for the differences in results although there are some reports of antianginal effect at lower doses.

The duration of antianginal effect demonstrated in this study is probably also a dose-related phenomenon with the prolonged efficacy reflecting, in part, the high doses used. Reichek and associates, using nitroglycerin ointment, Winsor and Berger, using oral controlled release nitroglycerin, and Lee and associates, using ISDN capsules, have reported antianginal efficacy for 3 hours or longer. Glancy and associates also reported improved exercise time to angina at 2 hours after oral ISDN. In contrast, the hemodynamic and antianginal effects of sublingual nitroglycerin have generally been found to be less than 1 hour in duration.

Consideration solely of mean data obscures some very pertinent information about individual patient response. It is clear that there was a very wide range of response in exercise times to ISDN. Some patients showed dramatic improvement while in others, ISDN may have had a detrimental effect. Attempts to classify patients as good responders are necessarily arbitrary, particularly in the absence of multiple retests to limit random scatter of exercise times in individual patients. Thus, figures for the number of patients who were good responders or poor responders are only rough approximations. It is quite clear from the data that the exercise response to ISDN was not uniform.

Additional light is shed on this problem when the response to sublingual nitroglycerin is considered. The exercise response to sublingual nitroglycerin is a good predictor of the response to oral ISDN. Six of 21 patients (29%) failed to respond (less than 25% net increase in exercise time) to either drug. These patients might thus be termed nitrate nonresponders rather than oral ISDN nonresponders. That some patients with angina pectoris will not have a beneficial response to nitrates, including sublingual nitroglycerin, has long been recognized but curiously overlooked in many studies evaluating long-acting nitrates.

A number of factors need to be considered as explanations for these therapeutic failures. It is important to give an adequate dose of nitrate. Although we used only a single standard dose of sublingual nitroglycerin, we deliberately maximized ISDN doses in an attempt to eliminate therapeutic failures due to insufficient dosage of ISDN. Significant heart rate and blood pressure changes occurred in the subgroup of patients who showed a poor exercise response (< 25% improvement) after oral ISDN. Significant heart rate and blood pressure changes also occurred in the patients who showed a poor exercise response after sublingual nitroglycerin. These hemodynamic changes suggest that inadequate dosage is not the explanation for the therapeutic failure of nitrates in these particular patients.

An overdose of nitrates might also prevent the beneficial effect on exercise performance, but the pattern of response was not suggestive of a nitrate overdose in any patient. A plausible but untested hypothesis for the therapeutic failure of nitrates in some patients is that the net effect of the complex nitrate-induced hemodynamic alterations does not change or influences adversely the balance of myocardial oxygen supply and demand.

A consideration of untoward effects is in order when using ISDN doses of the magnitude employed in this study. Marked changes in resting blood pressure and heart rate recorded in the sitting position occurred at its peak effect. In only one instance did any adverse effect occur as a result of these hemodynamic changes. Patient 13 complained of lightheadedness while sitting on the bicycle immediately prior to his exercise test 1 hour after ISDN administration. His blood pressure at this time was 84/74 mm Hg as compared to a control blood pressure of 114/89 mm Hg. The patient was allowed to lie supine for several minutes before proceeding with the exercise test. His exercise time increased by 134% compared to the control value.

Headaches occurred in seven of 21 patients (33%) following sublingual nitroglycerin and in 10 of 21 patients (48%) following ISDN. In several of these patients, headaches occurred only while exercising. The headaches following ISDN were most frequent and of greatest intensity approximately 1 hour after the ISDN dose. However, six of the 10 patients who experienced headache had at least a mild headache during the exercise test 5 hours after ISDN. In no instance did headache interfere with the testing protocol or require cessation of exercise.

Some caution is advised about conclusions to be drawn from these data. The demonstration of improved exercise tolerance following a single dose of a nitrate drug does not establish its long-term efficacy. Indeed, there is need for caution regarding the use of drugs which produce chronic vasodilatation. The industrial medicine literature is replete with descriptions of withdrawal syndromes in workers chronically exposed to nitrate powder and vapor.

In addition to this problem of dependence, there is evidence of tolerance developing to nitrate effects including the common observation of rapid tolerance to nitrate-induced headaches. Until more information is available regarding the long-term effects of high doses of nitrates, we feel that caution is advised for continuous nitrate prophylaxis, particularly in patients with only mild angina pectoris.

Evaluation of nitrates as antianginal agents is difficult. Variations in study protocol, doses utilized, and the population of patients studied have probably all contributed to the long-standing controversy regarding nitrates. This study, as well as other recent studies, establishes that orally administered ISDN has a prolonged hemodynamic effect as well as a prolonged antianginal effect. However, not all patients with angina pectoris benefit from oral ISDN. Further work is needed to predict which patients will have a
good antianginal response. Further work is also required to establish the efficacy and safety of the long-term use of ISDN when given in effective doses.

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