Oral Isosorbide Dinitrate in the Treatment of Angina Pectoris

Dose-Response Relationship and Duration of Action During Acute Therapy

UDHO THADANI, M.B.B.S., HO-LEUNG FUNG, PH.D., ANDREW C. DARKE, PH.D., AND JOHN O. PARKER, M.D.

with the statistical assistance of Margery J. Cruise, M.Sc.

SUMMARY The duration of effects of single oral doses of 15, 30 and 60 mg of isosorbide dinitrate (ISDN) were studied in 12 patients with stable, exercise-induced angina pectoris. The effects of a 120-mg dose were also studied in seven of these 12 patients. The average peak values for plasma ISDN concentration were 6.8, 14.3, 17.5 and 26.0 ng/ml after 15, 30, 60 and 120 mg of ISDN, respectively, and there was a 5-, 12-, 6-, and 5-fold interindividual variation in peak plasma concentration at these doses. At rest, both the systolic and diastolic blood pressures decreased after each dose of ISDN in both the supine (p < 0.05) and standing (p < 0.01) positions. The reduction in systolic blood pressure was more marked in the standing position. This effect occurred at 1 hour and persisted for 6 hours after 15 mg of ISDN and for 8 hours after other doses of ISDN. Exercise duration to the onset of angina and to the development of moderate angina increased by a similar degree after each dose of ISDN compared with placebo values (p < 0.001). This was apparent by 1 hour and the effects persisted for 8 hours. The maximum increase in walking time to angina occurred after 15 mg in six patients, after 30 mg in two patients, and after 60 mg in three patients. One patient did not improve after any of the doses. The heart rate (p < 0.01) and rate-pressure product (p < 0.05) at the onset of angina after any dose of ISDN increased compared with placebo values. However, ST-segment depression at the onset of angina was similar after ISDN and placebo. At the onset of moderate angina, the values for rate-pressure product after ISDN were similar to those after placebo, but ST-segment depression was less after ISDN (p < 0.05).

These data show that administration of single doses of ISDN from 15–120 mg increased exercise tolerance to angina for 8 hours, but for the whole group, higher doses did not have a quantitative greater effect on exercise tolerance than the lower doses.

SUBLINGUAL GLYCERYL TRINITRATE is the most often used antianginal agent. Taken prophylactically, it prolongs exercise tolerance in both the upright and supine positions. However, the therapeutic efficacy of long-acting oral nitrates in patients with angina pectoris has been controversial. In 1975, Aronow reported that the long-acting nitrates had little therapeutic merit. Recently, however, it was shown that isosorbide dinitrate (ISDN), given orally in large doses, had prolonged hemodynamic effects in patients with heart failure and improved exercise tolerance in patients with angina pectoris during both acute and long-term therapy. However, many of the important issues of therapeutic relevance are unanswered. Specifically, the dose-response relationship during acute and sustained therapy and the duration of action of different doses of ISDN in angina pectoris are not well defined. Furthermore, the correlation between the therapeutic effects and plasma ISDN levels is not known. This investigation was designed to determine the effects of acute administration of ISDN in patients with angina pectoris. The preliminary results of this work were recently published in abstract form.

Methods

Thirteen male patients, ages 42–70 years (average 57 years) with stable, exercise-induced angina pectoris, were studied. The history of angina ranged from 6 months to 5 years (average 14 months) and was induced solely and repeatedly by exercise in all patients. None of the patients were hypertensive or had clinical or radiologic evidence of cardiac enlargement or failure. None was taking drugs other than sublingual glyceryl trinitrate, and this was not required on the days of the investigation. Four of the patients had suffered a myocardial infarction at least 6 months before the study. Coronary angiography was performed in seven of the remaining nine patients and
had shown evidence of luminal narrowing of 75% or more of two or more coronary arteries.

The resting ECG was normal in nine patients and showed ST-T-wave changes in the inferior leads in the remaining four patients. During preliminary treadmill exercise testing, all patients developed horizontal or downsloping ST-segment depression in modified lead V₅ of 0.1 mV or more of at least 0.08 second duration. The study was explained and informed, written consent was obtained from each patient.

During preliminary studies 24–48 hours before the definitive investigations, each patient walked on a motor-driven treadmill using the Bruce multistage protocol. The patients were instructed to indicate the point at which definite chest pain developed (onset of angina) and the point at which the pain became of such severity which necessitated discontinuation of exercise (angina of moderate severity). The study group was selected from patients who had chest pain by the end of stage 2 or beginning of stage 3 during treadmill exercise.

Precautions were taken to control factors that could produce changes in exercise tolerance. The laboratory temperature was 20–22°C, and the patient’s apprehension was reduced by familiarization with the technique and staff.

**Design of Investigation**

The definitive studies were performed in the morning after an overnight fast and during the days of the investigation the patients did not smoke. The study was double-blind and placebo-controlled. Each patient was studied twice a week for 3 weeks with the studies separated by 3-day intervals. Patients taking part in the study were randomly allocated to one of the three groups shown in table 1. Studies were started at 0830 hours (control study), when heart rate, blood pressure, and ECG were recorded at rest in the supine and standing positions and during treadmill exercise. Then, each patient took 15 mg of ISDN or placebo and the measurements made at rest and during exercise at 1, 2, 4, 6, and 8 hours after the medication.

The end point during exercise for the control study was the development of angina of moderate severity; after placebo or ISDN, the end point was angina of moderate severity, fatigue or undue breathlessness. At 2½ hours after initiation of the study, the patients ate a light meal without coffee. Each patient was restudied in the same manner on four other days with increasing doses of ISDN (30, 60 and 120 mg) or placebo. Placebo was randomly administered as shown in table 1. In addition, on the last day, each patient was studied before and after the second placebo. The placebo tablets and ISDN tablets were identical in appearance.

If symptomatic hypotension developed on day 1 or 4, the patient was withdrawn from the study; if it developed on day 7 or later, the patient remained in the study, but the dose of ISDN was not increased and he was restudied only after the second placebo.

**Measurements and Recordings**

Modified lead V₅ was monitored on an oscilloscope throughout the study and records were taken on a standard ECG at a paper speed of 25 mm/sec at 1-minute intervals for 2 minutes in the supine and standing positions and at 1-minute intervals during exercise. Further records were taken at the onset of angina and when angina became of moderate severity. The average values for heart rate and ST-segment depression during 10 consecutive beats were measured from the ECG. Blood pressure was measured using sphygmomanometry at 1-minute intervals at rest and during exercise. The rate-pressure product was calculated as the product of heart rate multiplied by systolic blood pressure and was expressed in mm Hg·min⁻¹ × 10².

Venous blood (8 ml) was collected at rest before each exercise period for determination of plasma ISDN concentration. Blood was collected in tubes containing EDTA, spun in a refrigerated centrifuge at 3000 rpm at 3°C within 5 minutes of sampling, and the plasma stored at −20°C. Plasma ISDN levels were measured by a gas chromatographic method, which is a modification of the method described for determining plasma nitroglycerin concentration. In our laboratory, the variation in plasma ISDN concentration with replicate measurements with this method is less than 10%. With the plasma sample of 0.2 ml, this method is sensitive to plasma concentration of 0.1 ng/ml or greater.

Conventional statistical methods were used throughout. Significance of changes was studied by analysis of variance and the significance of results determined using a multiple range test. As five of the 12 patients did not receive a 120-mg dose, separate analysis was performed with 12 patients for placebo and the 15-, 30- and 60-mg doses and with seven patients for placebo and the 15-, 30-, 60- and 120-mg doses.

**Results**

One patient felt lightheaded and lost consciousness transiently 1 hour after the first oral dose of 15 mg of ISDN. His systolic blood pressure dropped from 120 mm Hg to 60 mm Hg in the standing position, but increased to 80 mm Hg in the supine position. The ECG showed sinus bradycardia but was otherwise normal. This patient was not given further doses of ISDN and
been excluded from the study. Of the remaining 12 patients, all were studied after placebo and 15, 30 and 60 mg of ISDN, and seven of the 12 patients were also studied after 120 mg of ISDN. Five patients did not receive a 120-mg dose because they experienced lightheadedness at the 60-mg dose. The study was completed in these 12 patients without serious complications.

Plasma ISDN Concentration

The time course of plasma ISDN concentration for the whole group after each dose of ISDN is shown in figure 1. The mean plasma peak concentrations were observed at 1 hour, 30 minutes, 2 hours and 2 hours after 15-, 30-, 60- and 120-mg ISDN doses, respectively. The average peak values were 6.8, 14.3, 17.5, and 26.0 ng/ml after 15, 30, 60, and 120 mg of ISDN, with a 5-, 12-, 6-, and 5-fold interindividual variation in peak plasma concentrations at these doses. Furthermore, plasma concentration peaked at different times in different patients after similar doses of ISDN. Plasma concentration peaked at 30 minutes in five, at 1 hour in five and at 2 hours in two patients after both 15 and 30 mg of ISDN, at 30 minutes in three, 1 hour in one patient and at 2 hours in eight patients after 60 mg of ISDN, and at 30 minutes in one patient, at 1 hour in two, at 2 hours in two, and at 4 hours in two patients after 120 mg ISDN.

Adverse Effects

None of the patients had angina at rest and none required glyceryl trinitrate tablets for angina precipitated during exercise.

Eight patients experienced transient lightheadedness after ISDN; in five this occurred after the 60-mg dose and in three, it developed after 120 mg. These symptoms occurred 2–4 hours after oral ingestion of the drug and disappeared on assumption of the supine position. One of these eight patients had presyncope 3 hours after 60 mg ISDN, but this was reversed on assumption of the supine posture.

Exercise Tolerance (tables 2 and 3, figs. 2 and 3)

Exercise was discontinued because of moderately severe angina during the control studies and the series of exercise tests after placebo 1 and placebo 2. After placebo 1 and 2, exercise duration to the onset of angina pectoris (AP1) and to the development of angina pectoris of moderate severity (AP2) did not change significantly from the respective pre-placebo control values (fig. 2).

After ISDN, exercise duration to AP1 and AP2 was prolonged in 11 of the 12 patients after the 15-mg dose, in 10 of the 12 patients after 30 mg, in eight of the 12 patients after the 60-mg dose, and in six of the seven patients after the 120-mg dose. All patients developed AP1 after each dose of ISDN, but two patients did not develop AP2 until exercised 4 hours after ISDN 30 and 60 mg. In these patients, exercise was discontinued because of fatigue and the exercise time to fatigue was substituted for AP2. Thus, after each dose of ISDN, walking time to AP1 and AP2 increased significantly compared with the values after placebo (p < 0.001) (fig. 2). This improvement in exercise tolerance was apparent within 1 hour and persisted for 8 hours after 15, 30, 60 and 120 mg of ISDN compared with the corresponding placebo values (p < 0.01) (fig. 2). Exercise duration to AP1 and AP2, 4 hours after placebo or ISDN was consistently less than the duration of exercise at 2 or 6 hours (fig. 2). This was presumably because the patients were fed 2½ hours after ingestion of placebo or drug. The average data (fig. 2 and table 2) show that after 60 and 120 mg of ISDN, patients exercised longer than after 15-mg doses. However, when daily variations in exercise duration to AP1 and AP2 observed during the control studies were taken into consideration, we found that the increase in average walking time to AP1 and AP2 after 15, 30, 60 and 120 mg were similar.

In any given patient, walking time to angina during the control studies varied from one day to another, so the data were normalized by calculating the percent-
TABLE 2.  Clinical, Electrocardiographic and Circulatory Data During Exercise

<table>
<thead>
<tr>
<th>TWT (seconds)</th>
<th>Hours After Oral Dose</th>
<th>ST-segment depression (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>AP1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo1</td>
<td>255</td>
<td>293</td>
</tr>
<tr>
<td>±25</td>
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<tr>
<td>Placebo2</td>
<td>274</td>
<td>304</td>
</tr>
<tr>
<td>±22</td>
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</tr>
<tr>
<td>ISDN</td>
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<tr>
<td>15 mg</td>
<td>218</td>
<td>404</td>
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<tr>
<td>±21</td>
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<tr>
<td>30 mg</td>
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<td>425</td>
</tr>
<tr>
<td>±22</td>
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<tr>
<td>60 mg</td>
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</tr>
<tr>
<td>±26</td>
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</tr>
<tr>
<td>120 mg</td>
<td>297</td>
<td>465</td>
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<tr>
<td>±36</td>
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</tr>
</tbody>
</table>

| AP2           |    |    |    |    |    |    |               |    |    |    |    |    |    |
| Placebo1      | 331| 384| 390| 354| 365| 387|               | 2.7| 2.9| 2.9| 3.0| 3.0| 2.9|
| ±28           |    |    |    |    |    |    |               |    |    |    |    |    |    |
| Placebo2      | 384| 408| 403| 366| 391| 402|               | 2.9| 2.9| 2.9| 3.0| 3.0| 2.7|
| ±25           |    |    |    |    |    |    |               |    |    |    |    |    |    |
| ISDN          |    |    |    |    |    |    |               |    |    |    |    |    |    |
| 15 mg         | 334| 456| 443| 401| 410| 415|               | 2.8| 2.1| 2.1| 2.3| 2.3| 2.5|
| ±31           |    |    |    |    |    |    |               |    |    |    |    |    |    |
| 30 mg         | 364| 475| 484| 430| 458| 455|               | 2.7| 2.0| 2.1| 2.5| 2.7| 2.7|
| ±30           |    |    |    |    |    |    |               |    |    |    |    |    |    |
| 60 mg         | 365| 489| 481| 441| 466| 463|               | 2.6| 1.8| 1.7| 2.2| 2.3| 2.3|
| ±25           |    |    |    |    |    |    |               |    |    |    |    |    |    |
| 120 mg        | 393| 503| 490| 459| 474| 488|               | 3.0| 2.4| 2.1| 2.7*| 2.4| 3.1|
| ±47           |    |    |    |    |    |    |               |    |    |    |    |    |    |

Data are mean ± SEM.
Abbreviations: AP1 = onset of anginal pain; TWT = treadmill walking time; HR = heart rate; SBP = systolic blood pressure; ISDN = isosorbide dinitrate; AP2 = onset of moderately severe chest pain.
p values in comparison to placebo values. * = < 0.05; † = < 0.01.

age changes in walking time after drug or placebo on any given day by the following formula:

walking time to angina after drug -
walking time to angina before drug
walking time to angina before drug

The average percentage increase in walking time to AP1 after ISDN 15, 30, 60, and 120 mg were similar. Similar calculations were also made for AP2 and the percentage increase in walking time to AP2 after ISDN 15, 30, 60 and 120 mg were also similar.

To take the placebo effects into account, the percentage change in walking time to AP1, at any given hour after placebo was subtracted from the percentage changes in walking time to AP1 after drug at the identical hour to obtain the net percentage change in walking time to AP1 after the drug. The individual values for the maximum percentage increase in walking time to AP1, irrespective of time after the ingestion of the drug, are shown in figure 3. Improvement in net walking time to AP1 by 25% or more after 15, 30, and 60 mg ISDN was observed in 11, 11 and nine patients, respectively. The maximum increase in walking time to AP1 occurred after 15 mg in six patients, after 30 mg in two patients, and after 60 mg in three patients. Three patients improved less after the 60-mg dose than after the 15- or 30-mg dose. Of the seven patients who also received 120-mg doses, exercise tolerance improved by 25% or more in six, but four of these six patients had less improvement in walking time after this dose than that after the 15- or 30-mg dose.

The individual data was also analyzed for AP2. Eleven, nine and eight patients had improvement in walking time to AP2 by 25% or more after 15, 30, and 60 mg of ISDN, respectively. The maximum increase in walking time to AP2 occurred after 15 mg in seven patients, after 30 mg in two patients, and after 60 mg in two patients. Three patients improved less after the 60-mg dose than after the 15- or 30-mg dose. Of the
seven patients who also received 120 mg of ISDN, exercise tolerance improved by 25% or more in five, but four of these five patients experienced less improvement in walking time after this dose than after the 15- or 30-mg dose.

Electrocardiographic ST-segment Changes (tables 2 and 3)

During exercise in the six control studies and after placebo 1 and 2, 11 of the 12 patients developed ST-segment depression of 1 mm or more at the onset of angina, and this became more pronounced at AP2. During each exercise period, ST depression at AP1 and AP2 after placebo 1 and 2 was similar to the control exercise period (table 2). ST-segment depression at AP1 was similar after placebo and any given dose of ISDN. However, when ST segments were assessed after ISDN at the same duration of exercise when angina had occurred during the placebo studies, there was significantly less ST-segment depression after each dose of ISDN for up to 4 hours (p < 0.05). At AP2, ST-segment depression was less pronounced after any given dose of ISDN compared with the placebo values (p < 0.05). The reduction in ST-segment depression at AP2 after ISDN was apparent for 4 hours after 15- and 30-mg doses and for 6 hours after 60- and 120-mg doses.

Examination of individual values showed that ST-segment depression was less pronounced both at AP1 and AP2 after any given dose of ISDN in nine of the 12 patients.

Circulatory Changes at Rest (tables 2 and 3, figs. 4 and 5)

Resting blood pressure in the supine and standing positions was not altered after placebo 1 and 2 (figs. 4 and 5). However, after each dose of ISDN, systolic blood pressure decreased significantly compared with the placebo values (p < 0.001) (figs. 4 and 5). At 1 hour the reduction in systolic blood pressure was more marked in the standing position, and this effect persisted for 8 hours (fig. 5). The reduction in standing systolic blood pressure at 4, 6, and 8 hours after ISDN 60 and 120 mg was greater than that after ISDN 15 mg (p < 0.05) (fig. 5). Similarly, reduction in systolic blood pressure at 4 and 6 hours after 60 and 120 mg was greater than after the 30-mg dose (p < 0.05).
Compared with placebo, diastolic blood pressure decreased after each dose of ISDN both in the supine \((p < 0.05)\) and standing \((p < 0.01)\) positions (figs. 4 and 5). Resting heart rate in the supine position did not change significantly after any of the doses of ISDN, but was higher in the standing position compared with the placebo values \((p < 0.001)\) (fig. 5).

**Circulatory Data During Exercise (tables 2 and 3; fig. 6)**

Group data for heart rate and systolic blood pressure during exercise are shown in table 2. Compared with placebo, patients exercised to a higher heart rate after any given dose of ISDN \((p < 0.001)\), but the values for systolic blood pressure at the onset of AP\(_1\) or the development of AP\(_2\) did not change significantly after any given dose of ISDN. Compared with placebo, the rate-pressure product at AP\(_1\) increased significantly after ISDN \((p < 0.05)\), but the values for this parameter at AP\(_2\) were similar after placebo and ISDN.

At AP\(_1\), the rate-pressure product increased at 1 and 2 hours after the ISDN 15-mg dose, at 1, 2, 4, 6 and 8 hours after the ISDN 30- and 60-mg doses and at 1 and 2 hours after ISDN 120-mg dose (fig. 6).

**Discussion**

Our results show that ISDN administered orally was rapidly absorbed from the gastrointestinal tract and exerted sustained hemodynamic and antianginal effects. The drug produced a dose-related reduction in resting systolic blood pressure. This effect was more marked in the standing than the recumbent position. The effects of the drug on treadmill walking time to angina were, however, not dose- or plasma-concentration-related; a single dose of 15 mg produced an improvement in exercise performance similar to that seen after single doses of 30, 60 and 120 mg. Before these results can be put into their proper perspective, it is necessary to examine the methods in the present study. Patients were carefully selected and all had stable angina pectoris. Such a selection may impose limitations in applying the results to a broader clinical population, but is necessary for meaningful comparison of drug effects in such a complex clinical syndrome as angina pectoris.

The studies involved repeated exercise testing over 3 weeks, which could have influenced the exercise performance of patients owing to a training effect. This fact was taken into account in designing the study and during the 3-week period, each patient was studied after placebo twice; the first placebo was administered randomly and the second was given on the last day of the study. The drug effects were considered significant only if these were different from the values after both the first and second placebos.
TABLE 3. (Continued)

<table>
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<th>ATAP₁</th>
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<tr>
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<td>F  p</td>
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</table>

**FIGURE 2.** Duration of action of single oral doses of 15, 30 and 60 mg of isosorbide dinitrate (ISDN) in 12 patients and 120 mg in seven patients with angina pectoris. Data are mean ± SEM. Compared to placebo, walking time to the onset of angina pectoris (AP₁) and to the development of moderately severe angina pectoris (AP₂) increased significantly after each dose (p < 0.001). This effect was apparent by 1 hour (p < 0.001) and persisted for 8 hours (p < 0.01) after each dose. The increase in walking time to AP₁ and AP₂ was similar after each dose.
The study can be criticized in that the different doses of ISDN were not administered in a random order. Such an approach would be ideal, but in view of the hypotensive effects of the drug, we elected, for patient safety, to double the doses of ISDN only if no symptomatic hypotension developed.

A truly double-blind trial in an investigation like this, in which the active drug had effects on resting blood pressure, which were different from the placebo, is difficult. To minimize the bias, the investigator was not aware of the dose sequence of ISDN administered in a given patient and the first placebo was administered in a random order. Despite these limitations, the results have important implications.

In the present study, oral ISDN was rapidly absorbed and the plasma levels increased in proportion to the amount of the oral dose. Although the present results cannot quantitate the extent of ISDN first-pass metabolism, oral ISDN was not completely biotransformed by the liver during its passage through the hepatic circulation. These findings are in agreement with a recent report in which plasma levels peaked at 30 minutes after a single oral dose of 5 mg of ISDN.

At rest, the hypotensive effects of ISDN were more marked in the standing than in the supine position and were greater at higher doses. These findings are in agreement with a previous report in which the effects of low doses (5-10 mg) and high doses (20 mg) were studied in six patients. In the present study, the hypotensive effects of oral ISDN were present at 1 hour and the effects persisted for 8 hours after any given dose. The reduction in systolic blood pressure was associated with a consistent increase in heart rate only in the standing position. These findings and those reported in previous studies are in contrast to the reports by Needleman and colleagues, who found that nitrates administered orally or into the hepatic vein of rats had no pharmacologic effects and suggested that the nitrates were rapidly inactivated by the liver enzymes of these animals. Our studies suggest that in man, ISDN is rapidly absorbed after oral administration, does not undergo complete first-pass transformation, and exerts significant pharmacologic effects.

Although sublingual glyceryl trinitrate prolongs exercise tolerance in patients with angina pectoris, the usefulness of long-acting nitrates, including ISDN in angina pectoris, was until recently seriously questioned. In one study, 10 mg of sublingual ISDN prolonged exercise tolerance after 10 minutes but had no effect after 1 hour, and the drug was considered to be no more effective than sublingual nitroglycerin.

Many other studies showed that small doses of ISDN...
(5–10 mg) administered sublingually or orally were no better than placebo. In recent studies, however, after the oral administration of large doses of ISDN, its pharmacologic effects on hemodynamics in patients with heart failure persisted for 3–7 hours. These reports stimulated interest in long-acting nitrates as antianginal agents and in four recent reports, single oral doses of 20–50 mg of ISDN were shown to prolong exercise tolerance for 2–5 hours in patients with stable angina pectoris. However, in none of these studies were the effects of different doses of ISDN on exercise tolerance evaluated in the same individuals. In the present study, improved exercise tolerance of 25% or more was observed in 11 patients after a dose of 15 mg, in 11 patients after a dose of 30 mg, and in nine patients after a dose of 60 mg occurred. Of the seven patients who also received 120-mg doses, exercise tolerance improved in six of seven patients. One patient did not improve after any of the doses. The improvement in exercise tolerance was present at 1 hour after the oral dose, and the beneficial effects persisted for 8 hours after each dose in the present study. More important, near-maximum improvement occurred after a single dose of 15 or 30 mg of ISDN in the majority of patients, and little further was gained by increasing the doses to 60 or 120 mg. For the group, the increase in exercise tolerance seen after the high doses of 60 and 120 mg ISDN was similar to the increase in exercise tolerance after the smaller doses of 15 and 30 mg. However, only seven patients were studied after the 120-mg dose. Our data do not provide an explanation as to why higher doses of ISDN do not have quantitatively greater effects on improving exercise tolerance than lower doses. Possibly, with the doses given in the present study, one was observing a plateau of response. Had we given doses lower than 15 mg, we might have been able to demonstrate the standard type of S-shaped dose-response curve.

The improved exercise tolerance was associated with a significant reduction in ST-segment depression in nine of the 12 patients, a finding in agreement with previous reports. In the present study, patients could exercise to higher heart rates after each dose of ISDN, and these findings are in agreement with earlier reports with this agent in patients with angina pectoris. In previous reports, the effects of ISDN on the rate-pressure product during exercise have been conflicting. Some workers have reported higher rate-pressure

FIGURE 4. Duration of action of single oral doses of 15, 30 and 60 mg of isosorbide dinitrate (ISDN) in 12 patients and 120 mg in seven patients on heart rate and blood pressure in the supine position. Data are mean ± SEM. Systolic (p < 0.01) and diastolic (p < 0.05) blood pressure decreased after each dose of ISDN compared with placebo. The reduction in systolic blood pressure persisted for 8 hours after each dose. No significant changes in heart rate occurred.
products\textsuperscript{14,15} while others have reported no change in this parameter after ISDN compared with placebo.\textsuperscript{16} In the present study, the rate-pressure product at the onset of angina increased significantly after ISDN compared with the values after placebo. On the other hand, the values of rate-pressure product at the onset of moderate angina were similar after either ISDN or placebo.

Heart rate and systolic blood pressure are important determinants of myocardial oxygen requirements, but these two variables do not take into account the influence of ventricular volume and myocardial contractility, which are important determinants of myocardial oxygen requirements. Nitrates have been shown to reduce ventricular end-diastolic volume and dimensions in the upright position both in normal subjects and in patients with angina pectoris\textsuperscript{21} However, Goldstein and co-workers\textsuperscript{35} have shown that sublingual glyceryl trinitrate-induced decrease in end-diastolic dimensions diminished substantially during exercise. In their six patients with angina pectoris, ventricular end-diastolic dimensions during exercise decreased substantially in two patients and by less than 4% in the remaining four. It has also been shown that nitrates improve systolic function in hypokinetic segments during supine exercise\textsuperscript{41} and reduce left ventricular end-diastolic pressure.\textsuperscript{48} Glyceryl trinitrate-induced reduction in left ventricular end-diastolic pressure may improve subendocardial perfusion and augment collateral blood flow to the ischemic areas.\textsuperscript{44} In the present study, and in previous studies in patients with angina pectoris,\textsuperscript{13-18} the effects of ISDN on ventricular volumes, contractility or filling pressure were not measured. Therefore, we cannot comment on the overall effects of different doses of ISDN on the myocardial oxygen supply-and-demand equation in the patients studied.

Our results show that the majority of patients with stable angina pectoris showed maximum improvement in exercise tolerance after single oral doses of 15 and 30 mg of ISDN. Furthermore, prolonged antianginal effects persisted for at least 8 hours after single doses of 15, 30, 60 and 120 mg of ISDN, but a dose-response relationship did not exist. However, in view of the development of tolerance to the circulatory effects during chronic therapy with nitrates,\textsuperscript{88-42} caution should be exercised in extending these results to sustained therapy.
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