Clinical and Circulatory Effects of Isosorbide Dinitrate

Comparison with Nitroglycerin


SUMMARY

In order to resolve current controversies on isosorbide dinitrate (ISDN), we employed a particularly sensitive testing protocol to evaluate effects of sublingual ISDN and nitroglycerin on the exercise capacity of patients with angina. Ten minutes after ISDN 21 of 23 patients exercised longer (average 2.7 minutes, \( P < 0.001 \)) than after placebo. Benefit was evident in only a minority of patients tested one hour and in none tested two hours after either ISDN or nitroglycerin. A given amount of exercise resulted in lower mean blood pressure (average 13 mm Hg, \( P < 0.001 \)), higher heart rate (average 10 beats/min, \( P < 0.001 \)), and shorter ejection time (average 0.04 second, \( P < 0.001 \)) after ISDN. Similar changes were seen after nitroglycerin. The product of blood pressure, heart rate, and ejection time, an index of myocardial O\(_2\) consumption, was unchanged at angina after ISDN or nitroglycerin despite the increased exercise capacity, suggesting that clinical improvement after these drugs may be due to circulatory changes causing decreased myocardial O\(_2\) demand. We conclude that sublingual ISDN closely resembles nitroglycerin in its alteration of circulatory responses to exercise and in the duration of the resultant improvement in exercise capacity.

**Additional Indexing Words:** Isosorbide dinitrate        Angina pectoris        Nitroglycerin

Despite their widespread use the efficacy and mode of action of the so-called “long-acting” nitrates remain a source of controversy. Of this group of drugs, isosorbide dinitrate (ISDN), administered sublingually, appeared to offer particular promise because of its relatively greater ability to enhance the exercise capacity of patients with angina pectoris.\(^1\)-\(^3\) The effectiveness of this drug, however, has been questioned by other investigators, who failed to demonstrate any improvement following either sublingual or oral ISDN.\(^4\)-\(^6\)

Seeking to resolve this controversy, we studied the influence of sublingually administered ISDN on the exercise performance of patients with angina pectoris. Our approach differed fundamentally from methods of previous investigators as follows: (1) We employed a particularly sensitive exercise protocol which we have shown to be reliable in identifying alterations in the exercise capacity of patients with angina produced by various interventions.\(^7\) (2) We chose drug dosages for each subject on the basis of physiologic response in the resting state. (3) We obtained direct, continuous measurement of circulatory parameters closely related to myocardial oxygen demand, thus permitting a comparison of clinical performance with those physiologic

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alterations likely to influence the precipitation of angina. Using these methods, we evaluated the time course of both symptomati
cic and circulatory changes associated with the administration of ISDN. Furthermore, to
determine if this drug is truly “long-acting,”
we compared the duration of action of ISDN
with that of nitroglycerin. We also assessed
the acute effects of nitrates on exercise
performance before and after long-term ISDN
treatment to determine if chronic exposure to
this drug impaired patient responsiveness to
nitrates.

Methods

Twenty-three patients exercised until the onset
of angina before and at varying lengths of time
after treatment with placebo, ISDN, or nitroglyc
erin. Patients ranged in age from 34 to 67 years
(median 52 years). Although ten had either type
II or type IV hyperlipoproteinemia, none had
overt diabetes, hypertension, clinically apparent
disease of cerebral or peripheral arteries, or any
significant complicating medical condition. Each
patient had had stable, typical angina pectoris for
at least six months prior to study. Twenty-two
had evidence of one or more acute myocardial
infarctions, and all of the 17 individuals who had
coronary arteriography were found to have
greater than 75% narrowing of one or more
coronary arteries. Of the 12 patients who had left
ventriculography, nine had areas of akinesia, and
four had chamber enlargement. Ten patients were
receiving digitalis, but none was in overt
congestive heart failure.

Patients participating in this study were chosen
from those individuals admitted to the National
Heart and Lung Institute for evaluation and
therapy of angina. Despite evidence of severe
coronary occlusive disease, many of these individu
als led moderately active lives, and some worked
full-time. Elderly patients and patients with
associated diseases were excluded in the course of
selecting candidates for admission to the National
Heart and Lung Institute. However, we do not
feel that this selection process was likely to
influence our results or conclusions.

Patients exercised in the upright position on a
Godart bicycle ergometer until the onset of
angina or until the development of leg fatigue
sufficient to preclude further exercise. Work load
was increased 20 w every three minutes; load at
outset was chosen individually so that each
patient developed angina from three to six
minutes after starting. The appropriateness of the
work levels chosen and the consistency of patient
performance were confirmed in each instance by
preliminary trials on the ergometer in the absence
of any drug on at least two different days.

During the definitive study intra-arterial press
ture was measured through a Coumand needle in
the brachial artery or through a no. 5 Eley cath
with end and side holes positioned so that its tip
lay in the descending thoracic aorta. The
electrocardiogram was also recorded continuously,
using apical-manubrial or apical-subscapular bi
coranar chest leads. At least 15 minutes of rest were
interposed between successive bouts of exercise.
All studies were performed three or more hours
after meals or cigarette smoking. No patient was
receiving propranolol or long-acting nitrates at
the time of study (except when the influence of
chronically administered ISDN was being as
sessed). Patients received either ISDN or a
sublingual lactose placebo* ten minutes prior to
initiating exercise. Despite its physical resemblance to ISDN, both investigators and patients
were able to distinguish placebo from ISDN by its
lack of hemodynamic effects and their sequelae
flushing, tachycardia, etc.). Therefore, patients
were told that the placebo was an agent different
from ISDN; however, they were not informed
that this agent was pharmacologically inert. The
dosage of ISDN chosen was the minimum amount
sufficient to produce a 10-mm Hg fall in mean
blood pressure and/or a 10-beat/min rise in heart
rate while at rest in the sitting position. Twelve
patients requiring 10 mg of ISDN while the
remaining 11 were given 5 mg. Those patients
receiving nitroglycerin were given this drug three
minutes before exercising. Dosages of nitroglyc
erin were chosen in the same manner as dosages
of ISDN.

ISDN (or, in some instances, nitroglycerin)
was always given prior to the third bout of
exercise, placebo being given prior to the first or
second bout. Using the same exercise protocol, we
have shown that exercise capacity and the
circulatory response to exercise are not altered
materially by previous bouts of exercise when as
many as six serial bouts of exercise are
performed. Thus, we did not anticipate that the
two previous bouts of exercise would significantly
affect results obtained during exercise after
ISDN. Although it would have been desirable to
alternate the sequence of ISDN and placebo
studies, administration of drug prior to placebo
was not feasible because the delay required for
the effects of the nitrate to dissipate would have
prolonged the study excessively.

*Both ISDN (Isordil) and the placebo were
supplied by Ives Corp., New York, N. Y.
In addition to the studies just described, we also compared the effects of ISDN, nitroglycerin, and placebo on the maximum width of the cardiac silhouette on 6-ft posterioranterior X-rays taken during bicycle exercise performance in the upright position. After three minutes of submaximal exercise, each patient was instructed to stop breathing at the end of a normal inspiration but, at the same time, to continue exercising. As soon as the patient stopped breathing, an X-ray was taken, which was synchronized with the electrocardiogram to occur at end-diastole. X-rays obtained in this manner were judged acceptable only if the variation of the level of the diaphragm between placebo and drug studies was less than 1.5 cm. Ten duplicate X-rays obtained at rest in the absence of drug therapy showed an average difference (±1 sd) of 1.2 mm ± 1.5 (0.8% ± 1.0) between successively determined estimates of the maximum width of the cardiac silhouette.

Results

Effects of Placebo

Prior treatment with placebo failed to alter significantly exercise capacity, time to onset of ST depression, or any of the measurements of the circulatory response to exercise (fig. 1).

Effects of ISDN on Exercise Capacity and Electrocardiogram

Comparison of exercise capacity after ISDN and after placebo (fig. 2) showed that 21 out of 23 patients were able to pedal at least one minute longer after ISDN. The mean increment in exercise capacity was 2.7 minutes (P < 0.001). Sixteen patients were able to perform work against a greater load before experiencing angina, and nine were limited by fatigue rather than by angina following ISDN. Only two patients exercised less after ISDN than after placebo.

Measurements of the time to onset of ischemic electrocardiographic change provided a more objective criterion of improvement in those individuals who exhibited such changes in the monitored leads. In a typical example (fig. 3), the onset of ischemic change, defined as a horizontal depression in
the ST segment of 0.5 mm or more from baseline, was noted after two minutes of exercise following placebo. After ISDN ischemic changes did not begin until the fifth minute of exercise. Of the 11 patients with ischemic changes in the monitored leads, ten experienced a delay in the onset of these changes (fig. 4) averaging 3.4 minutes ($P < 0.001$). Electrocardiographic changes during exercise in the five patients receiving cardiac glycosides at the time of study were delayed after ISDN to the same extent as electrocardiographic changes in the remaining six patients not receiving cardiac glycosides. The time of onset of ischemic electrocardiographic change did not alter appreciably during serial exercise trials when no drug treatment was given.

The time course of improvement in exercise capacity following ISDN was investigated by having patients exercise at varying time intervals after treatment (fig. 5). The greatest increase in exercise capacity was observed during the first exercise period after the sublingual administration of ISDN. This improvement waned rapidly, however, so that by one hour after ISDN, only 4 of 11 patients continued to exhibit an increase in exercise capacity of one minute or more. None of the patients tested two hours after treatment manifested an increase in exercise capacity. Similarly, a delay in onset of ischemic electrocardiographic changes during exercise after sublingual ISDN was evident for less than one hour in five out of six patients.

In eight individuals serial exercise testing was performed after nitroglycerin, and when exercise capacity and circulatory response to exercise returned to baseline, serial exercise testing was repeated after ISDN administration. The similarity of results obtained whether or not ISDN was preceded by nitroglycerin suggested that performance after ISDN was unaffected by the antecedent nitroglycerin. Comparison of the duration of action of the two drugs tested in the same individuals (fig. 6) showed that in most instances the beneficial effects of ISDN on exercise capacity lasted no longer than those of nitroglycerin.

### Effects of ISDN on Circulatory Changes During Exercise

The increase in exercise capacity and the delay in onset of ischemic electrocardiographic changes furnished both subjective and objective evidence of improvement after ISDN. In order to investigate the possible reasons for this improvement, we examined circulatory responses to exercise after placebo and after ISDN. Particular emphasis was placed on factors important in determining myocardial demand for oxygen. In each patient comparisons were made between measurements after equal duration of exercise. Measurements made at angina during exercise
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Figure 3

An example of the delay in onset of ischemic electrocardiographic change during exercise following ISDN. Serial electrocardiograms using lead CM5, shown here at one-minute intervals, exhibited definite ST depression after two minutes of exercise following placebo (upper panel) while a similar degree of ST depression was not observed until the patient had exercised for five minutes following ISDN (lower panel).

Figure 4

Comparison of the time of onset of 0.5 mm or more ST depression during exercise following placebo (circles on the left) and following ISDN (circles on the right). Lines connect the values for each individual. Dashed lines indicate the three-minute intervals when work load was increased. The mean increment, 3.4 minutes, is shown by the two circled bars.

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Figure 5

The time course of changes in exercise capacity following ISDN as evaluated by serial exercise trials. For each individual, exercise capacity after placebo (left) is connected to corresponding values of exercise capacity assessed at several times after ISDN. Exercise trials terminated because of the onset of angina are indicated by closed circles while those stopped because of leg fatigue are designated by open circles. The scale on the horizontal axis denotes the time elapsed after ISDN administration. Dashed horizontal lines indicate the intervals when work load was increased.
Comparison of the influence of ISDN and of nitroglycerin on exercise capacity assessed at varying times after treatment (top). Increment of exercise capacity above the level attained after placebo is shown on the vertical axis. The shaded bars denote mean values of this increment at each time period following treatment with vertical intersecting lines representing the standard error of the mean. Asterisks denote those mean values which are significantly different (P < 0.05) from zero. Numbers above the bars indicate the number of patients tested at each time period (exclusion of those individuals not tested at every time period does not materially alter the results). Doses of ISDN and nitroglycerin matched to produce similar circulatory effects at rest resulted in similar increment in exercise capacity initially. This increment tended to disappear at approximately the same rate for both drugs. Because of the roughly exponential character of this disappearance, a linearizing logarithmic transformation was performed on the increments. Regression lines fitted to the transformed data (bottom) were indistinguishable for the two drugs—the half-times for the increments in exercise capacity associated with either ISDN or nitroglycerin (TNG) were virtually identical.

Nineteen of 23 patients had lower mean arterial pressures when exercising after ISDN (fig. 7, left); the average decrease was 13 mm Hg. Only two individuals had higher mean pressures during exercise after ISDN. One of these also failed to have any increase in exercise capacity after ISDN. Systolic arterial pressure like mean pressure was lower after ISDN, but diastolic pressure was virtually unchanged.

The decrease in blood pressure during exercise seen after ISDN was accompanied by a consistent rise in heart rate, averaging 10 beats per minute, and a consistent decrease in ejection time, averaging 0.04 second or 17% (fig. 7). Examination of the circulatory responses in the one patient (designated by asterisks in fig. 7) to experience a marked deterioration of exercise capacity following ISDN revealed a slight rise in blood pressure and a very marked rise in heart rate during exercise after ISDN. The additional oxygen cost of the excessively rapid heart rate and the unusual rise in blood pressure during exercise (despite a fall in blood pressure at rest) probably explains why angina was precipitated much earlier in this one individual following ISDN.

A decrease in blood pressure and ejection time and increase in heart rate similar to that after placebo were matched to measurements made after the same duration of exercise following ISDN (generally prior to the onset of angina). The onset of angina was never associated with an abrupt change in any of the variables measured—use of measurements made just prior to angina rather than at onset of angina would therefore not have changed the results.
Comparison of mean blood pressure, heart rate, and (in those individuals who had aortic catheterization) ejection time during exercise after placebo and after ISDN. Values measured during exercise after placebo are connected to values observed after an equal amount of exercise following ISDN. Measurements made at onset of angina are indicated by closed circles, while measurements made after matching amounts of exercise (but not associated with angina) are indicated by open circles. Asterisks identify data obtained from the one patient who exhibited a marked deterioration in exercise capacity after ISDN. Average changes are shown by the circled bars on either side of each panel.

Comparison of mean blood pressure, heart rate, and ejection time during exercise after placebo and after nitroglycerin (TNG), analogous to material presented for ISDN in figure 7.

following ISDN was observed during exercise after nitroglycerin (fig. 8).

Since blood pressure and heart rate are both important determinants of myocardial oxygen requirements, the product of these two quantities is often used as an index of myocardial oxygen consumption. Pressure-rate product was significantly higher at the onset of angina after treatment with either ISDN or nitroglycerin (fig. 9, left). These results might suggest that the two drugs increased myocardial oxygen delivery, possibly through a direct effect on coronary circulation. However, since the time during
Pressure-rate product and triple product (blood pressure × heart rate × ejection time) at onset of angina during exercise after placebo and after either ISDN or nitroglycerin (TNG). Data from the same patients are shown in each panel. Values related to ISDN testing are identified by circles connected by solid lines and those related to nitroglycerin testing by triangles. Means are shown at either side of each panel. Pressure-rate product at angina (left) was significantly greater after either nitroglycerin or ISDN. When these same values are multiplied by ejection time (right), the resulting triple products at angina are the same after ISDN or nitroglycerin as they are after placebo.

Serial exercise testing revealed that alterations in blood pressure, heart rate, and ejection time after equal exercise following ISDN diminished with time in parallel with the disappearance of the increase in exercise capacity. Despite these changes triple product at angina remained constant throughout the series of exercises.

In addition to blood pressure, heart rate, and ejection time, ventricular size is also known to exert an influence on myocardial oxygen requirements.\textsuperscript{11, 12} Nitroglycerin has been shown to decrease ventricular dimensions during supine exercise.\textsuperscript{13} In our subjects measurement of maximum width of the cardiac silhouette during equal amounts of upright sublingual exercise (fig. 10) demonstrated a significant decrease in over-all cardiac size when either ISDN (average 2.3\%, P < 0.025) or nitroglycerin (average 2.1\%, P < 0.05) was compared with placebo. Similarly, decreases occurred while sitting at rest (average 3.8\% after ISDN and 3.6\% after nitroglycerin, P < 0.001).

Results After Chronic Treatment with ISDN

The acute effects of ISDN on exercise performance in ten patients regularly receiving sublingual ISDN (5 to 10 mg qid) were compared with the effects achieved when the patients had been on placebo. Six individuals were given ISDN for ten days prior to study, while the other four remained on treatment for one to seven months. In six randomly selected patients the course of placebo preceded ISDN; in four, a one- to two-week course of placebo followed ISDN. The rate of nitroglycerin consumption in any patient during therapy with either ISDN or placebo fluctuated widely; there was no consistent
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Figure 10

Maximum width of the cardiac silhouette after placebo and after ISDN compared at rest (left) and during exercise (right). Means are denoted by the circled bars.

difference between the two treatment periods. Exercise testing was initiated at least two hours after the last regular dose of either ISDN or placebo. No significant difference was observed in baseline exercise capacity after chronic treatment with ISDN. Blood pressure and heart rate responses and pressure-rate product at angina were also the same after chronic ISDN and after placebo. Moreover, the chronic administration of ISDN did not alter the usual response to the drug when administered acutely. Ten minutes after the sublingual administration of ISDN, the same increase in exercise capacity, the same changes in blood pressure and heart rate, and the same pressure-rate product at angina occurred whether the patient had been chronically taking ISDN or placebo. Individuals receiving chronic ISDN for more prolonged periods showed no tendency to behave differently from those receiving a relatively short course of ISDN. There was thus no evidence that chronic ISDN treatment altered either baseline exercise performance or responsiveness to sublingual ISDN when administered acutely.

Discussion

Our studies indicate that sublingual ISDN, administered in sufficient quantity to alter resting blood pressure and heart rate, produced a significant increase in exercise capacity in almost all patients. Subjective improvement was accompanied by a delay in the onset of ischemic electrocardiographic abnormalities. These changes were associated with consistent alterations in the circulatory response to upright exercise: a given amount of exercise resulted in lower systolic and mean blood pressures, a more rapid heart rate, and a shorter ejection time after ISDN. Over-all heart size (as assessed by cardiac silhouette) was also slightly reduced.

The increase in exercise capacity persisted for an hour or more in only a third of our subjects and was undetectable in any subject two hours after ISDN treatment. Similar results were obtained regarding the time of onset of ischemic electrocardiographic change. The duration of action of ISDN in most instances was not notably longer than that of nitroglycerin. The circulatory effects of ISDN and nitroglycerin were also very similar. Thus, it would not appear justified to single out sublingual ISDN as an antianginal agent of consistently greater merit than nitroglycerin.

Previous comparisons of ISDN and nitroglycerin\textsuperscript{1-3} have suggested that ISDN was significantly superior. Our results may differ because we used drug dosages matched to cause similar circulatory changes at rest. Patients given an arbitrary, fixed dose of nitroglycerin\textsuperscript{1-3} may not have received as much of this agent as we administered in our study (often 0.6 to 0.8 mg). The apparent superiority of ISDN demonstrated by others may merely represent a quantitative difference, which disappears when comparison is made with equipotent doses of ISDN and nitroglycerin.
The short duration of action of ISDN may account for the failure of some investigators to document efficacy when testing an hour or more after sublingual ISDN administration. In addition, several other aspects of this investigation may have been responsible for the differences between our results and the results of studies in which ISDN was found to be ineffective. Since different individuals require different dosages of the drug to produce a physiologic effect, we were careful to give each patient an amount of ISDN sufficient to alter resting hemodynamics. In addition, we used an exercise protocol which we have found, through extensive testing, to be reliable and sensitive in identifying alterations in the exercise capacity of patients with angina pectoris. We also compared responses to placebo and to ISDN at the same session, thereby obviating fluctuations in patient performance which are likely to occur when exercise periods are separated by days or weeks. Finally, since blood pressure is difficult to measure precisely during exercise using indirect methods and since blood pressure falls toward resting levels very rapidly when exercise is terminated, we utilized only the directly measured and continuously recorded exercising intra-arterial pressure in the assessment of the effects of ISDN on blood pressure during exercise.

The results of our investigation demonstrate that chronic administration of sublingual ISDN in usual clinical dosages (5 to 10 mg

Figure 11

Example illustrating the action of ISDN. The triple product (systolic blood pressure × heart rate × ejection time) on the vertical axis is represented as a function of the duration of exercise, shown on the horizontal time scale. Levels of work load are indicated by the shaded areas, while dashed vertical lines denote times of work load increment. Asterisks represent the onset of angina. The two solid lines show the changes in triple product during the course of exercise preceded by no treatment (slightly higher asterisk) and during exercise preceded by placebo (slightly lower asterisk). As illustrated by the dashed line, a given amount of exercise after ISDN resulted in a lower triple product. The patient was able to exercise for a considerably longer period and could perform work against a greater load prior to the onset of angina. Angina eventually did occur, however, when the patient reached the same limiting level of triple product associated with the onset of angina in the absence of ISDN.
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Such an analysis may be overly simplified since the triple product does not take into account potentially important influences affecting myocardial oxygen requirements, such as the inotropic state of the heart or left ventricular size, which may change significantly after ISDN or nitroglycerin. These agents might also act to change myocardial oxygen delivery: blood flow to ischemic regions of the myocardium might either be augmented as a result of coronary vasodilation or reduced secondary to the decrease in systemic (and thus coronary) perfusion pressure. Should ISDN or nitroglycerin produce major change in myocardial oxygen delivery or utilization by any of these mechanisms, a corresponding increase or decrease in the triple product at the onset of angina would logically be anticipated. The complete absence of change in the triple product at angina following ISDN or nitroglycerin suggests that alterations in these factors are not sufficiently important to change myocardial oxygen requirements significantly and that the improvement in exercise capacity caused by these drugs is primarily related to alterations in myocardial oxygen demands due to changes in blood pressure, heart rate, and ejection time. The possibility remains, however, that ISDN and nitroglycerin do cause significant changes in ventricular size, myocardial contractility, and myocardial perfusion and that the constancy of the triple product at angina occurs only because these changes fortuitously cancel out.

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