Clinical and Circulatory Effects of Isosorbide Dinitrate

Comparison with Nitroglycerin

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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 symptomatic 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 nitroglycerin. 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 individuals 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 onset 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 pressure was measured through a Coumand needle in the brachial artery or through a no. 5 Elecath 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 bipolar 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 assessed). 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 nitroglycerin 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.
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Comparison of exercise capacity (left) evaluated after no medication and after placebo. Dashed lines show the three-minute intervals when work load was increased. The mean differences, indicated by the circled bars on either side of the panel, were not significant. Placebo was administered in random order so that 11 patients received placebo before the first exercise and 12 received placebo before the second exercise. Mean pressure, compared after equal amounts of exercise (right), was similarly unaltered by prior treatment with placebo.

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 posteroanterior X-rays taken during bicycle exercise performance in the upright position. After three minutes of subanginal 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.8 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

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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.

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.

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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.

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
which the ventricle contracts may also influence myocardial oxygen consumption,\textsuperscript{10} correction was made for changes in the duration of systole by employing the triple product of blood pressure $\times$ heart rate $\times$ ejection time.\textsuperscript{7, 9} The resulting index, obtained at angina, was unaltered by ISDN or nitroglycerin (fig. 9, right), even though most individuals experienced angina after a considerably longer period of exercise.

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 subanginal 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

\textbf{Figure 9}

Pressure-rate product and triple product (blood pressure $\times$ heart rate $\times$ 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.
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 diastolic blood pressures, a more rapid heart rate, and a shorter ejection time after ISDN. Overall 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 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 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.\textsuperscript{4,14} 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.\textsuperscript{7} 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

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qid) does not alter clinical or physiologic responsiveness to the drug. Thus, nitrate tachyphylaxis, previously reported in man,15, 16 does not appear to be an important problem when ISDN is administered in the manner employed in this study. On the other hand, no persisting benefit in baseline exercise capacity resulted from prolonged use of ISDN.

Neither age nor sex nor baseline exercise capacity significantly modified the changes in exercise capacity and circulatory function after nitrate administration. For this reason we feel that our conclusions apply to the great majority of patients with angina due to coronary occlusive disease despite certain selection factors (e.g., the exclusion of the elderly or severely debilitated mentioned previously.

Knowledge of the circulatory changes associated with angina permits an evaluation, albeit somewhat incomplete, of the possible mechanism of action of ISDN in augmenting exercise capacity. The decrease in blood pressure and in ejection time and any decrease in ventricular size all tend to diminish myocardial oxygen demands.17 This tendency is opposed by the increase in heart rate. The constancy of the triple product (an index of myocardial oxygen demand) at the onset of angina suggests that the oxygen-sparing effects of decreased blood pressure and ejection time after ISDN are sufficient to offset the oxygen cost of the greater heart rate. Our data indicating that nitroglycerin appears to act by a similar mechanism are in agreement with results of others.18 The effect of ISDN on circulatory function is exemplified in figure 11, a plot of the triple product of systolic blood pressure × heart rate × ejection time during the course of exercise. Following ISDN the triple product rises more slowly, but angina occurs when the triple product reaches the same critical level. Thus, ISDN appears to enhance exercise capacity by lowering triple product (and, presumably, myocardial oxygen demand) at any given level of exercise, but ISDN treatment does not permit the patient to exceed that value of the triple product previously associated with the onset of angina.

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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