Hemodynamics and Antianginal Effects of High Dose Oral Isosorbide Dinitrate After Chronic Use

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SUMMARY In a randomized, double-blind, crossover study, 19 patients with angina were exercised 2 min after 0.4 mg sublingual nitroglycerin and after sublingual placebo and before and 1, 3, and 5 hours after oral isosorbide dinitrate (ISDN) and oral placebo. After initial testing, patients took the dose of ISDN they had had during the study (mean dose 29 mg) for a mean period of 5.6 months before retesting using the same protocol.

Compared to placebo, exercise time after sublingual nitroglycerin increased 56% (P < 0.001) initially and 51% (P < 0.001) at retest. Compared to placebo, exercise time increased 58% (P < 0.05) initially and 58% (P < 0.005) at retest 1 hour after ISDN, 38% (P < 0.05) initially and 27% (P < 0.005) at retest 3 hours after ISDN, and 13% (NS) initially and 21% (P < 0.02) at retest five hours after ISDN. The mean exercise times initially and at retest were not significantly different.

Hemodynamic changes (decrease in systolic blood pressure and increase in heart rate) at 15 min persisted through 300 min after ISDN during both initial testing and during retesting. However, these changes were significantly less during retesting. We conclude that a partial tolerance to the hemodynamic effects of the drug develops after chronic use of high dose oral ISDN but that the antianginal efficacy of both sublingual nitroglycerin and oral ISDN is unimpaired.

ORALLY ADMINISTERED ISOSORBIDE DINITRATE (ISDN) has sustained hemodynamic effects when given acutely.1,2 Our own recent study also demonstrated that a majority of patients with angina pectoris will have a sustained anti-anginal effect after high dose oral ISDN.3 Unfortunately, such acute studies do not establish the long-term efficacy of ISDN. Side effects may prevent chronic use or tolerance may develop to the therapeutic effects.

Tolerance may develop with the chronic use of nitrates. Rapid tolerance to nitrate-induced headaches has been commonly observed,4-7 and tolerance to the hemodynamic effects of nitrates has been documented.8-9 Concern has been raised not only for the development of tolerance to the therapeutic effect of long-acting drugs such as oral isosorbide dinitrate but also for crossover tolerance impairing the efficacy of sublingual nitroglycerin. Previous studies have not shown tolerance to the antianginal effects of nitrates when used chronically.10-12 However, the doses of nitrates used in many of these studies were small and probably inadequate to produce chronic vasodilatation. The high doses of ISDN which we employed in our recent study may be double-edged swords, and "carry within them the seeds of their own therapeutic failure via the development of tolerance."13

This study was designed to answer two questions regarding the chronic use of oral ISDN in patients with angina pectoris: Will adverse side effects prevent the chronic use of high doses of oral ISDN? Will tolerance to the therapeutic effects

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of ISDN develop after chronic use? To answer these questions, we put the study patients on chronic oral ISDN therapy after acute testing. The same patients were then re-studied using the same protocol.\(^1\)

**Methods**

**Patient Selection**

Twenty-one men between 42 and 64 years of age with typical effort angina pectoris were studied. Twenty of these 21 patients had either a history of clearly documented myocardial infarction and/or coronary angiographic demonstration of greater than 70% luminal narrowing in at least one major coronary artery. The other patient had coronary angiographic evidence of severe three-vessel disease documented after the initial testing. No patient had clinically evident congestive heart failure, hypertension (blood pressure \(\geq 150/100\) mm Hg), or liver disease prior to initial testing.

**Initial Testing**

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. 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 V\(_6\) were recorded by telemetry in the sitting position before exercise, at the end of exercise, 30 seconds 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. The ST-segment response during and after exercise was measured from the electrocardiographic recordings. The maximal amount of ST-segment depression below the resting level at 0.08 sec after the J point was determined as well as the duration of ST-segment depression \(\geq 1.0\) mm below the resting level. Blood pressures were recorded using a mercury sphygmomanometer with the patient in the sitting position before exercise and at the end of exercise.

Test doses of oral ISDN were administered on hospital days 1 to 3, but none was given for at least 16 hours prior to exercise testing. ISDN dosage was individually determined by development of 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 and minimize headaches or a precipitous fall in blood pressure. All patients had at least a 10 mm Hg 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 performed two exercise tests with two hours 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 with the patient in the sitting position immediately prior to drug administration and 2 min later, immediately prior to exercise.

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.\(^\dagger\) In addition to blood pressure and heart rate determinations prior to and during each exercise test, blood pressures and heart rates were measured in seated patients at 15, 30, 45, 90, 120, 150, 210, 240, and 270 min after oral drug administration.

**Follow-Up Interval**

Following the initial study, patients were returned to whatever non-nitrate cardiac medications they had received prior to the testing plus oral ISDN. Seventeen of the 21 patients were on propranolol therapy. Patients were followed with periodic outpatient visits. An attempt was made to use chronically the same dose of ISDN used in the initial study. Patients bothered by headaches during initial testing were discharged on lower doses of ISDN with a gradual increase in dose to the study dose over a 2 to 3 week period. Patient 13 took ISDN three times daily. All other patients took the ISDN four times daily. This usually amounted to a dose every four hours while awake. The doses of ISDN used during the follow-up interval are listed in table 1.

Patient 9 was unable to tolerate chronic oral ISDN therapy even in doses of 5 mg four times daily. He complained of fatigue and nausea and felt the medication had no antianginal efficacy. His ISDN was discontinued. Patient 3 admitted he occasionally did not take his ISDN because of headaches. The other 19 patients all reported regular use of ISDN and were closely questioned on this point at each follow-up visit. During the period between studies, no other nitrates were used except for sublingual nitroglycerin when needed for chest pain.

During the follow-up period, patient 13 developed mild congestive heart failure and was begun on digoxin and hydrochlorothiazide. Patient 8 was resuscitated by para-

\(^*\)Warren E. Collins, Inc., Braintree, Massachusetts.

\(^\dagger\)Oral ISDN and oral placebo of identical appearance were supplied through Dr. Clarence Denton, Ives Laboratories, New York, New York.
CHRONIC USE OF ISOSORBIDE DINITRATE/Danahy, Aronow

TABLE 1. Clinical Data

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Mean* 28.9 27.4 5.6

*Excludes patients 7 and 9.
†Dose taken four times daily, except for patient 13 who took dose three times daily.

Abbreviations: ISDN = isosorbide dinitrate.

medics from an episode of ventricular fibrillation. Evidence was equivocal for a subendocardial infarction at this time. The patient returned to his previous clinical status following this event which occurred three months prior to follow-up testing. None of the other patients experienced significant clinical events in the period between studies.

Follow-Up Testing

Nineteen of the original 21 patients were retested. Patient 9, who could not tolerate the ISDN, and patient 7, who was unable to return for follow-up testing because of the demands of his job, were not retested.

All cardiac medications except for ISDN were stopped at least 72 hours prior to follow-up testing. The usual dose of ISDN was continued through 6 P.M. on the evenings prior to definitive testing and then held until testing was completed the following day.

Patients were hospitalized for the follow-up study. Two practice exercise tests were again performed by each patient prior to definitive testing. The exercise protocol was identical in every detail with that used initially. The control exercise times had improved in several patients and thus exceeded 6 min during the follow-up testing in four patients. The routine on the three days of definitive testing was also identical with the routine used initially (third through fifth hospital days as defined under Initial Testing). Regardless of the ISDN dose used chronically between studies, the individual dose of ISDN used for initial testing was used for follow-up testing in every patient (table 1).

The data were analyzed using Student's t-test for correlated means to determine significance levels. All comparisons between initial testing and follow-up testing were made on paired data from the same patients. Resting heart rate and blood pressure changes from the initial testing were recalculated after deletion of the data from the two patients who did not participate in the follow-up testing. Exercise times and end-exercise heart rate and blood pressure results from initial testing were recalculated after deletion of the data from these two patients as well as deletion of the data from patient 21.

Patient 21 completed follow-up testing but no longer experienced a consistent anginal endpoint during exercise. He exercised to exhaustion without developing angina during control tests. Therefore, his exercise data were excluded from analysis since there was no anginal baseline against which to measure drug-induced changes.

Results

Clinical data are illustrated in table 1. Headache was common initially but usually disappeared after 2 to 3 weeks of therapy. In those patients in whom headaches persisted, the headaches were generally mild and of little consequence to patients. Patient 3 did report persistent headaches of sufficient magnitude to interfere with his regular use of the medication while patients 7, 10, 13, and 17 required some reduction in dosage because of headaches.

These observations were made during the interval between tests when both the patients and the investigator were aware that ISDN was being used. However, they correspond closely to the observations made under double-blind conditions during the exercise testing. During initial testing, nine patients had headaches after ISDN while one patient had headaches after both ISDN and placebo. During follow-up testing, four patients had headaches after ISDN while one patient had headaches after both ISDN and placebo. During initial testing, many of the headaches were moderately severe while all of the headaches occurring during follow-up testing were very mild.

No patient had syncope but two patients (9 and 10) reported light-headedness with initial use. Two patients (9 and 12) described indigestion with initial use. Two patients (1 and 18) noted transient pruritis during therapy but this occurred after several months of treatment and disappeared spontaneously within a few weeks without any change in ISDN dosage. Patient 7 fractured a carpal bone during therapy and reported that the ISDN aggravated the throbbing pain in his wrist for the first several days after injury.

Mean exercise times for both initial and follow-up tests are illustrated in figures 1 and 2. Compared to placebo, the mean exercise time increased 121 sec at 1 hour after ISDN on initial testing ($P < 0.005$) and 129 sec on follow-up testing ($P < 0.001$), 74 sec at 3 hours after ISDN on initial testing ($P < 0.01$) and 70 sec on follow-up testing.
FIGURE 1. Mean exercise times ± 1 SEM before (C = control) and 1, 3, and 5 hours after oral placebo and before and 1, 3, and 5 hours after isosorbide dinitrate (ISDN). Data from initial testing are displayed on the left while data from follow-up testing are displayed on the right.

![Graph showing mean exercise time](image)

(P < 0.01), and 25 sec at 5 hours after ISDN on initial testing (NS) and 48 sec on follow-up testing (P < 0.05). Compared to placebo, the mean exercise time increased 114 sec after sublingual nitroglycerin on initial testing (P < 0.001) and 101 sec on follow-up testing (P < 0.001). There was no significant difference between any of these paired results on initial testing versus follow-up testing.

The exercise data were also analyzed by calculating a percentage change after sublingual nitroglycerin and a percentage net change after ISDN, as defined in table 2. This method of analysis gives a relatively greater weight to absolute changes in patients whose control exercise times are short. For example, a 1 minute increase in exercise time is a 33% increase when the control exercise time is 3 minutes but only a 16.5% increase if the control exercise time is 6 minutes. The mean percentage change after sublingual nitroglycerin was 56% (P < 0.001) initially and 51% (P < 0.001) at follow-up. The mean percentage net change was 58% (P < 0.05) initially and 58% (P < 0.005) at follow-up 1 hour after ISDN, 38% (P < 0.05) initially and 27% (P < 0.005) at follow-up 3 hours after ISDN, and 13% (NS) initially and 21% (P < 0.02) at follow-up 5 hours after ISDN. Once again there was no significant difference between initial and follow-up results.

The mean control exercise time increased from 236 seconds during initial testing to 292 seconds during follow-up testing. This difference of 56 seconds is significant (P < 0.02). There was no difference at follow-up testing in control measurements prior to ISDN as compared to control measurements prior to placebo for any parameter measured in the study.

While the mean exercise times showed similar changes during both initial and follow-up studies, there was considerable variation in individual exercise response. The well-recognized phenomenon of regression toward the mean is very apparent in these data. Several patients with excellent responses initially showed a diminished effect on retesting while several patients with poor responses initially had a good response on retesting.

If a 25% or greater net change is arbitrarily defined as a good response to ISDN, then four of 21 patients (19%) did not have a good response on either test (this includes the two patients with an initially poor response who were not retested). Using the same criteria of a ≥ 25% change after sublingual nitroglycerin, these same four patients plus two others (29%) did not have a good response to nitroglycerin on either test.

The depth of the ST-segment response to exercise and the duration of ST-segment depression after exercise were constant for the majority of patients, regardless of changes in the exercise time required to reach an anginal endpoint. None of the 19 patients showed a worsening of the ST-segment response after either ISDN or nitroglycerin during either study. During initial testing, the intensity and duration

![Graph showing mean exercise time](image)
of anginal discomfort was not significantly different, comparing nitroglycerin to placebo and comparing ISDN to placebo. At follow-up testing, the duration of angina was not significantly different comparing nitroglycerin and ISDN to placebo except for the test 1 hour after ISDN. At 1 hour after ISDN, the mean duration of angina was 35 seconds less than after placebo ($P < 0.05$).

The mean net changes in resting heart rate, systolic blood pressure, and diastolic blood pressure in the sitting position and their statistical significance are graphically displayed in figures 3–5. Significant net increases in heart rate occurred from 15 min through 300 min after ISDN during both phases of testing. During follow-up testing, the heart rate increases were consistently less than those seen initially. The mean net heart rate increase over the entire five hour study period was 10.2 beats/min initially as compared to 6.1 beats/min on

**FIGURE 3.** Mean changes $([\text{ISDN-control}]- (\text{placebo-control}))$ in resting heart rate in the sitting position $\pm 1$ SEM. Data from initial testing are plotted on the upper curve while data from follow-up testing are plotted on the lower curve. For follow-up testing, the points plotted as unfilled circles indicate a significant difference between ISDN and placebo; at 15 min, 45 min, and 240 min, $P < 0.05$; at 30 min, 60 min, 90 min, 210 min, and 300 min, $P < 0.01$. For the initial testing curve, the points plotted as unfilled circles indicate a significant difference between initial testing and follow-up testing, $P < 0.05$. 

**TABLE 2.** Percentage Change in Exercise Time After Sublingual Nitroglycerin and Percentage Net Change in Exercise Time After Oral Isosorbide Dinitrate

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<th>Pt. No.</th>
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<th>% change 1 hr after ISDN†</th>
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*% change after TNG = (TNG ET minus placebo ET) X 100
placebo ET

†% net change after ISDN = (ISDN ET minus control ET) X 100
control ET minus (placebo ET minus control ET) X 100
control ET

‡Data from pts 7, 9 and 21 are excluded.
Abbreviations: TNG = sublingual nitroglycerin; ISDN = oral isosorbide dinitrate; ET = exercise time.
follow-up testing. This difference of 4.1 beats/min is significant ($P < 0.001$).

Decreases in systolic blood pressure occurred from 15 min through 300 min after ISDN on retesting with significant changes, as compared to placebo, from 60 min through 300 min. Again, the changes in systolic blood pressure on retesting were consistently less than those seen initially. The mean decrease in systolic blood pressure over the entire five hour study period was 5.6 mm Hg initially and 8.7 mm Hg on follow-up testing, a difference of 4.3 mm Hg ($P < 0.001$).

The mean changes in diastolic blood pressure after ISDN were not significant on follow-up testing. On initial testing, a significant decrease in diastolic blood pressure was noted from 90 min to 270 min after ISDN. The mean decrease in diastolic blood pressure over the entire 5 hour study period was 1.3 mm Hg on initial testing and 1.1 mm Hg on follow-up testing, a difference of 0.2 mm Hg ($P < 0.05$).

The mean heart rate increase measured 2 min after sublingual nitroglycerin was 8.3 beats/min ($P < 0.001$) at follow-up testing, as compared to 9.9 beats/min ($P < 0.001$) at initial testing. The mean systolic blood pressure decrease measured 2 min after sublingual nitroglycerin was 7.1 mm Hg ($P < 0.02$) at follow-up testing as compared to 11.3 mm Hg ($P < 0.001$) at initial testing. The mean diastolic blood pressure decrease measured 2 min after sublingual nitro-
glycerin was 0.1 mm Hg at follow-up testing as compared to 2.1 mm Hg at initial testing. None of these differences between initial testing and retesting is significant.

At follow-up study, the end-exercise heart rate was 14 beats/min greater at 1 hour after ISDN as compared to placebo (P < 0.001), 5 beats/min greater at 3 hours after ISDN as compared to placebo (P < 0.02), and 4 beats/min greater at 5 hours after ISDN as compared to placebo (NS). At follow-up study, the end-exercise heart rate times systolic blood pressure was 3355 mm Hg beats/min greater at 1 hour after ISDN as compared to placebo, (P < 0.001), 1685 mm Hg beats/min at 3 hours after ISDN as compared to placebo (P < 0.02), and 693 mm Hg beats/min at 5 hours after ISDN as compared to placebo (NS). These end-exercise hemodynamics at follow-up testing are not significantly different from the results observed at initial testing.

Discussion

A major consideration in using high doses of oral ISDN chronically is whether patients will tolerate the side effects. As is clear from table 1, headache was a very common side effect. However, most patients developed partial or complete tolerance to headache within a few weeks. These results are in accord with numerous previous observations regarding nitrate-induced headaches either from therapeutic use6,7 or from industrial exposure.8 None of the 21 patients had to stop therapy because of headaches.

Propranolol therapy was reinstituted in 17 of the 21 study patients at the same time as chronic ISDN therapy was begun (the day after initial testing was completed). Relief from headaches may have been caused by the concomitant use of propranolol, a conclusion reached by several of our patients. While our data cannot be considered conclusive on this point, observations suggest that propranolol was not a crucial factor in reducing headaches. Most patients reported gradual reduction in headaches over a 1 to 2 week period, not a sudden change with the reinstitution of propranolol therapy. Furthermore, propranolol was gradually tapered and stopped completely at least 72 hours prior to follow-up testing while ISDN therapy was continued. There was no increase in headaches at this time.

Other side effects, as indicated in table 1, were uncommon. Nausea was a prominent symptom in the one patient who could not tolerate the ISDN. Dyspeptic symptoms may relate to relaxation of gastrointestinal smooth muscle, particularly in the lower esophageal sphincter. We conclude that although initial side effects are common, a large majority of patients will tolerate the chronic use of high doses of ISDN.

The exercise times in this follow-up study make it clear that high dose oral ISDN remains an effective antianginal therapy even after chronic use. We could detect no evidence of development of tolerance to the antianginal effect of the drug. Similarly, sublingual nitroglycerin remains effective after chronic use of ISDN.

We did not attempt to assess the efficacy of sublingual nitroglycerin while the patients were still receiving ISDN. We picked 14 hours as the time between the last dose of ISDN and the start of follow-up testing, for both ISDN and sublingual nitroglycerin. This was an attempt to make measurements after the ISDN had been metabolized or excreted, but before any ISDN-induced tolerance had dissipated. It is possible that there would be a reduced response to sublingual nitroglycerin if the evaluation was performed while the patient was already in a vasodilated state from a very recent dose of ISDN. From clinical assessment, this was not a problem as all study patients reported no change in the effectiveness of sublingual nitroglycerin used during chronic ISDN therapy.

Resting heart rate and blood pressure changes after ISDN were still readily demonstrable at follow-up testing but these changes were consistently and significantly diminished as compared to initial testing. Thus, these data demonstrate development of some tolerance to the hemodynamic effect after chronic use of ISDN. These results are very similar to those of Schelling and Lasagna who noted attenuation of the heart rate and blood pressure response to sublingual nitroglycerin during a four week course of oral pentaerythrol tetranitrate.9 The results of Schelling and Lasagna, as well as the rapid development of tolerance to nitrate headache, suggest that nitrate tolerance takes only a few weeks or less to develop. Animal studies have shown that tolerance will develop within a few days of regular nitrate administration with maximal tolerance occurring after a few weeks of exposure.10 The disappearance of tolerance followed a similar time course in these studies. There is evidence to indicate that tolerance to the vasodilator activity of organic nitrates involves an alteration in a receptor in vascular smooth muscle.11

It is somewhat incongruous that despite ample evidence of tolerance to nitrate effects the therapeutically important antianginal effects showed no evidence of attenuation. If one makes the plausible assumption that the antianginal effects of oral ISDN are mediated by hemodynamic effects, some attenuation of the antianginal effect would also be expected. We did not measure the effect of ISDN on several parameters which are important in mediating the antianginal effect of nitrates, including ventricular filling pressures,16-17 ventricular volumes,18 and ejection time.11,19 However, we speculate that some degree of tolerance does develop to the antianginal effects of oral ISDN but it is too subtle to be detected with our protocol.

Cohn has previously argued that measuring exercise capacity provides a less sensitive index of drug effect than hemodynamic changes.20 Goldstein and Epstein have noted that a hemodynamic effect from sublingual ISDN may persist at a time when an antianginal effect, as measured by bicycle exercise performance, could no longer be demonstrated.21 Data from our acute study demonstrate the same phenomenon; at 5 hours after oral ISDN, bicycle exercise performance showed a small but statistically nonsignificant increase. In contrast, hemodynamic effects were still readily apparent and highly significant at 5 hours after ISDN.

In our present study, we were able to further increase the sensitivity of heart rate and blood pressure measurements as monitors of nitrate effect by using a mean of all the measurements over the 5 hour study period. Using this method, we could demonstrate that the small, 2.9 mm Hg mean difference in systolic blood pressure was a highly significant change statistically. In contrast, the mean percentage net change in exercise time at 3 hours after ISDN decreased from +38% on initial testing to +27% on follow-
up testing and increased from +13% at 5 hours after ISDN on initial testing to +21% on follow-up testing. However, these differences were not statistically significant because of a relatively large standard error of the mean. Thus, we feel that in using our protocol, exercise performance is a less sensitive, though clinically more relevant measure of nitrate effect. Furthermore, we believe this difference in sensitivity is the explanation for the apparent inconsistency in hemodynamic versus antianginal results as regards demonstration of tolerance. Leaving aside this question of sensitivity of hemodynamic versus antianginal parameters, we do wish to emphasize what our data clearly does show, that large oral doses of ISDN produce a sustained antianginal effect even with chronic use.

Some concerns about the chronic use of large doses of nitrates remain, particularly regarding nitrate dependence. This adverse effect would be much more difficult to demonstrate in patients with angina than would nitrate tolerance. Deliberate attempts to demonstrate nitrate dependence would also raise serious ethical questions. However, the experience with munitions workers as reported by several investigators, and perhaps best documented by Lange and co-workers, establishes that anginal chest pain, coronary artery spasm, and sudden death may occur during withdrawal from chronic industrial exposure to nitrates.

In light of this industrial experience, as well as the clinical experience reported during interruption of propranolol therapy in anginal patients, we would strongly advocate gradual reduction rather than abrupt discontinuation of chronic, high dose nitrate therapy in anginal patients. We would also recommend that continuous nitrate antianginal prophylaxis not be used in patients whose symptoms are readily controlled with less intensive nitrate therapy.

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Hemodynamics and antianginal effects of high dose oral isosorbide dinitrate after chronic use.

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