Tolerance to the Circulatory Effects of Oral Isosorbide Dinitrate
Rate of Development and Cross-tolerance to Glyceryl Trinitrate

UDHO THADANI, M.B.B.S., DANTE MANYARI, M.D., JOHN O. PARKER, M.D.,
AND HO-LEUNG FUNG, PH.D.

SUMMARY The effects of 15, 30, 60 and 120 mg of isosorbide dinitrate (ISDN) on systolic blood pressure (SBP) and heart rate (HR) were compared after acute oral administration and during sustained therapy four times daily with ISDN in six patients. After any given dose, plasma ISDN levels were higher during sustained therapy than during acute therapy. The average peak reduction in standing SBP occurred at 2 hours after 15, 30, 60 and 120 mg of ISDN; the values were 39, 42, 45 and 46 mm Hg, respectively, after acute therapy and 21, 20, 26 and 24 mm Hg, respectively, during sustained therapy (p < 0.01). Compared with placebo, the reduction in SBP was still apparent 6 hours after any given dose of ISDN during acute but not during sustained therapy (p < 0.01). HR increased significantly only after acute therapy.

The rapidity of development of tolerance to ISDN and cross-tolerance to glyceryl trinitrate (GTN) was evaluated in eight other patients. The average peak reduction in SBP after the first dose of 15 mg of ISDN was 36 mm Hg, but after therapy with ISDN every 6 hours, the fifth dose of 15 mg of ISDN produced a peak reduction in SBP of only 7 mm Hg (p < 0.001). The first dose of 0.6 mg GTN before therapy with ISDN produced a peak reduction in SBP of 40 mm Hg, but after therapy with ISDN every 6 hours for 5 days, the same dose of GTN produced a maximum reduction in SBP of only 10 mm Hg (p < 0.001).

The results show that partial circulatory tolerance to ISDN and cross-tolerances to GTN developed rapidly during regular therapy with ISDN. The plasma ISDN concentrations were higher during sustained than after acute therapy, suggesting that the tolerance (tachyphylaxis) to nitrates in man is due to the diminution of the end organ response and not to the accelerated metabolism of nitrates.

NITRATES are often used to treat patients with angina pectoris and congestive heart failure. However, the development of tolerance during chronic therapy with these agents is of some concern. In animal experiments, the reduction in systemic arterial blood pressure induced by glyceryl trinitrate (GTN) is rapidly attenuated during continuous therapy with this agent. Furthermore, in rats, the induction of tolerance was found to be time- and dose-dependent. Needleman and Johnson reported that all organic nitrates, especially erythrityl tetrinitrate and mantel hexanitrate, induced tolerance to the circulatory effects of GTN; isosorbide dinitrate (ISDN) induced the least tolerance. In contrast to the reports in animals, the observations regarding the development of tolerance during nitrate therapy in man have been conflicting. Many workers have reported that during continuous therapy with organic nitrates, the headaches disappeared or diminished in intensity, and tolerance to the circulatory effects and cross-tolerance to GTN were usually well established within a few weeks. However, other workers have failed to show the development of circulatory tolerance to ISDN and cross-tolerance to GTN during sustained therapy with ISDN. This controversy is unresolved.

The present investigation was designed 1) to study the phenomenon of circulatory tolerance during oral ISDN therapy and to determine how rapidly this tolerance develops during continuous therapy; 2) to determine whether the development of tolerance to ISDN therapy is related to its accelerated metabolism; and 3) to investigate the development of cross-circulatory tolerance to GTN during continuous ISDN therapy.

Methods

Fourteen patients (12 males and two females) constituted the study population. All had stable angina pectoris due to coronary artery disease. Their ages ranged from 42–70 years (average 56 years). None were hypertensive or had unstable angina or were in heart failure. None had taken long-acting nitrates in the past and none were taking medications at the time of the study. The study was explained to each patient and written informed consent obtained.

Circulatory Effects of Isosorbide Dinitrate During Acute and Sustained Therapy

This part of the investigation was designed to compare the effects of 15, 30, 60 and 120 mg of ISDN on systolic blood pressure (SBP) and heart rate (HR) after acute and sustained oral therapy. Six patients were studied.

From the Division of Cardiology, Department of Medicine, Queen's University, Kingston, Ontario, Canada, and the Department of Pharmacetics, School of Pharmacy, State University of New York at Buffalo, New York.

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Address for correspondence: Dr. Udho Thadani, Department of Medicine, Eberhard Hall, Queen's University, Kingston, Ontario, Canada K7L 3N6.


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Acute Therapy

Each patient was studied at rest in the supine and standing positions on five different days over a period of 3 weeks. The studies were separated by at least 72 hours. On the days of the study, HR and blood pressure were recorded before and 1, 2, 4 and 6 hours after the administration of one of the doses of ISDN or placebo. Patients were given a light lunch after the 2-hour recordings were made. Doses of ISDN were 15, 30, 60 and 120 mg. Placebo was administered randomly, but for patient safety, ISDN dosage was increased only if no symptomatic hypotension developed with the previous dosage.

Sustained Therapy

After completion of the acute studies the patients were treated with placebo four times daily for 7 days. On day 8, the studies were repeated before and 1, 2, 4 and 6 hours after the morning dose of placebo. ISDN 15 mg was then prescribed four times daily for 7 days. On day 15, the studies described above were repeated before and after the morning dose of 15 mg of ISDN. The dose of ISDN was doubled at weekly intervals to a maximum of 120 mg four times daily, but before each increment, the studies were repeated before and after the morning dose of the drug. Thus, each patient was studied before and after placebo, ISDN 15 mg, 30 mg, 60 mg and 120 mg over 5 weeks.

Measurements and Recordings

Modified lead V̇ was recorded at 1-minute intervals for 2 minutes in the supine and standing positions. The average values for the HR during 10 consecutive beats were measured from the ECG and the blood pressure was measured by sphygmomanometry at 1-minute intervals.

Venous blood (8 ml) was collected in tubes containing EDTA for determination of plasma ISDN concentration at 0, ½, 1, 2, 4 and 6 hours after the administration of drug or placebo on each day. The total blood loss was 440 ml over a period of 8 weeks. The plasma was immediately separated and stored at −20°C. Plasma ISDN was measured by a gas chromatographic method. Analysis of the results of the above study showed that partial circulatory tolerance to ISDN was well established by 7 days.

Circulatory Tolerance to Isosorbide Dinitrate and Cross-tolerance to Glyceryl Trinitrate

This part of the investigation was designed to study the time required for the development of circulatory tolerance to ISDN during sustained therapy with this drug and to study the phenomenon of cross-tolerance to GTN. The drugs were prescribed at 6-hour intervals at specified times. Eight hospitalized patients were studied daily for 6 consecutive days after an overnight fast. The protocol described below is summarized in figure 1.

Day 1

The HR and blood pressure were measured in the supine and standing positions at 0800 hours, after which a placebo tablet was administered. The HR and blood pressure were measured in supine and standing positions at 0830, 0900, 1000, 1200 and 1400 hours. The patients were given a light lunch at 1215 hours. At 1400 hours, 0.6 mg GTN was administered sublingually, and HR and blood pressure response were measured at 1, 2, 5, 10 and 15 minutes. After completion of these observations, placebo tablets were administered at 1430, 2000 and 0200 hours.

Blood samples were collected in tubes containing GTN at 0800, 0830, 0900, 1000, 1200 and 1400 hours for ISDN concentration and at 1400, 1402, 1405 and 1410 hours for GTN concentration. Blood was centrifuged immediately and plasma stored in a frozen state for the determination of plasma ISDN or GTN concentration.

**Figure 1. Schematic diagram of the protocol for rapidity of development of circulatory tolerance to isosorbide dinitrate (ISDN) and cross-tolerance to glyceryl trinitrate (GTN). The arrows indicate the time when measurements were made.**
concentration. The plasma GTN was measured by a gas chromatographic method.27

Day 2

Control observations were repeated at 0800 hours, after which 15 mg of ISDN was administered orally and the dose repeated at 1400, 2000 and 0200 hours. HR and blood pressure were measured at 0830, 0900, 1000, 1200 and 1400 hours. Blood samples were collected before and ½, 1, 2, 4 and 6 hours after the morning dose of ISDN.

Subsequent Days

ISDN 15 mg was prescribed at 6-hour intervals as on day 2 and HR and blood pressure were recorded as on day 2, but no blood samples were obtained. This dosage was maintained until circulatory tolerance developed. Tolerance was defined as a 50% decrease in the magnitude of the maximal decline in SBP recorded after the initial dose of 15 mg of ISDN.

Once tolerance was observed, the control observations at 0800 hours were made and 30 mg of ISDN was administered and its effects on HR and blood pressure studied over a 6-hour period. During the remainder of the day, three doses of ISDN (30 mg) were administered at 1400, 2000 and 0200 hours.

If tolerance to 30 mg of ISDN developed during the first day of therapy with this dose, studies were repeated the following day before and for 6 hours after the administration of 60 mg of ISDN. During the remainder of the day, three doses of ISDN (60 mg) were administered at 1400, 2000 and 0200 hours. The studies were repeated the following day before and for 6 hours after the administration of 60 mg of ISDN. Blood samples were obtained for determination of ISDN level at 0800, 0830, 0900, 1000, 1200 and 1400 hours. At 1400 hours, i.e., 6 hours after the 60-mg dose, 0.6 mg GTN was given sublingually and its effects on HR and blood pressure were recorded at 1, 2, 5, 10 and 15 minutes. Blood samples for determination of GTN levels were collected at 1400, 1402, 1405 and 1410 hours.

Conventional statistical methods were used throughout. The changes in plasma ISDN concentration, HR and blood pressure were studied by analysis of variance, and the significance of the results was determined with the multiple range test.

Results

Circulatory Effects of Isosorbide Dinitrate During Acute and Sustained Therapy

Plasma Isosorbide Dinitrate

Figure 2 shows the mean plasma concentration after each dose of ISDN after acute and sustained therapy. Plasma ISDN concentrations at any given dose of ISDN were significantly higher during sustained than during acute therapy (p < 0.01).

![Figure 2. Time course of plasma isosorbide dinitrate (ISDN) concentration after 15, 30, 60 and 120 mg of ISDN administered acutely and during sustained therapy four times daily (six patients). Data represent mean ± sd. After any given dose of ISDN, plasma levels were higher during sustained than during acute therapy (p < 0.01). Readings at 0 hours during sustained therapy are values 12 hours after the dose taken the previous evening.](http://circ.ahajournals.org/}

Blood Pressure and Heart Rate

The group values for HR and SBP in the supine and standing positions after placebo and ISDN treatment are shown in table 1.

Acute Therapy

After acute oral administration of 15 mg of ISDN, SBP was significantly lower both in the supine and standing positions than the placebo values (p < 0.001), with the effects being more pronounced in the standing position (fig. 3). The reduction in standing SBP after 15 mg of ISDN occurred within 1 hour and persisted for 6 hours (fig. 3). ISDN 30, 60, and 120 mg produced a more marked reduction in standing SBP, which persisted for 6 hours (fig. 3). The reduction in SBP after each dose of ISDN was associated with an increase in HR that was significantly different from the placebo values only in the standing position (p < 0.01) (fig. 3).

Sustained Therapy

After therapy with 15 mg of ISDN four times daily for 7 days, SBP after the morning dose of 15 mg of
### Table 1. Circulatory Effects of Placebo and Isosorbide Dinitrate During Acute and Sustained Therapy

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<td>Values are mean ± sd. *p values are in comparison with corresponding placebo values.</td>
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<td>°p &lt; 0.05.</td>
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<td>Abbreviations: ISDN = isosorbide dinitrate; HR = heart rate; A = acute therapy; S = sustained therapy; SBP = systolic blood pressure.</td>
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TABLE 2. Effects of Placebo and Isosorbide Dinitrate Administered Every 6 Hours on Heart Rate and Systolic Blood Pressure

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<td>60 mg fifth dose</td>
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<td></td>
<td>SBP</td>
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Values are mean ± sd. p values are in comparison with placebo.  
*p < 0.05.  
†p < 0.01.  
‡p < 0.001.

Abbreviations: HR = heart rate (beats/min); SBP = systolic blood pressure (mm Hg); ISDN = isosorbide dinitrate.

ISDN was significantly lower in both the supine (p < 0.05) and standing (p < 0.01) positions than the placebo values. However, at any given time, the reduction in SBP was significantly less than that after acute therapy (p < 0.01) (fig. 3). Furthermore, after 1 week of therapy with 30, 60 and 120 mg of ISDN four times daily, the reduction in SBP after the morning doses of 30, 60 and 120 mg of ISDN was similar to that seen after 15 mg of ISDN (fig. 3). Compared with placebo, the reduction in SBP after 15, 30, 60 and 120 mg of ISDN was significant at 1, 2 and 4 hours (p < 0.01) but not at 6 hours (fig. 3). These changes in SBP were significantly different from those during acute therapy (p < 0.01) (fig. 3). The changes in HR during sustained therapy with ISDN were not significantly different from the corresponding placebo values (fig. 3). Four hours after the administration of placebo and all doses of ISDN, HR was higher than the corresponding pretreatment control values (p < 0.05) (fig. 3).

Adverse Effects

After acute oral administration of ISDN, three patients had severe headaches, which became less pronounced during sustained therapy in two of the three. Four patients had lightheadedness and nausea in the upright position after acute oral administration.
of 60 and 120 mg of ISDN. These symptoms were associated with a fall in SBP to 70 mm Hg or less. The symptoms, however, disappeared promptly on assumption of the supine position. None of the patients had such symptoms during sustained therapy.

Development of Circulatory Tolerance to Isosorbide Dinitrate

The group values for HR and SBP in the supine and standing positions during placebo and ISDN treatment are shown in table 2. The HR and SBP did not change significantly during the 6-hour observation period after placebo. After the first dose of 15 mg of ISDN, SBP decreased significantly both in the supine and standing positions compared with the values after placebo (p < 0.01), and the effects persisted for 6 hours; the reduction in SBP was more pronounced in the standing position. After the first dose of ISDN, HR increased in both positions, but achieved statistical significance only in the standing position (p < 0.01) (fig. 4). After therapy with 15 mg of ISDN every 6 hours, attenuation of the fall in SBP was observed within 1 day in six patients and within 2 days in the remaining two patients. Thus, within 48 hours of therapy with 15 mg of ISDN every 6 hours, circulatory tolerance to this drug had developed in all patients. The group values for SBP were significantly lower after the first dose than after the fifth dose of 15 mg of ISDN (p < 0.01) (fig. 4). Reduction in SBP was associated with an increase in HR after the first dose, but not after the fifth dose of 15 mg of ISDN (fig. 4). Further increments of ISDN doses to 30 and 60 mg over the next 3 days produced a fall in SBP similar to that which occurred with the fifth dose of 15 mg of ISDN (Table 2). There was a marked interindividual variation in the effects of the first dose of 15 mg of ISDN on HR and SBP. The data for two representative patients are shown in figure 5, which shows that the reduction in SBP after the first dose of ISDN (15 mg) was more pronounced in patient RS.
However, after regular treatment with ISDN for 5 days, 60 mg ISDN produced only a minimum reduction in SBP in both patients. This occurred despite the higher plasma ISDN levels after 60 mg of ISDN than after 15 mg of ISDN in both patients (fig. 5).

Cross-tolerance to Glyceril Trinitrate

The group values for HR and SBP in the supine and standing positions after the first dose of GTN during placebo therapy and after the second dose of GTN after 5 days of ISDN therapy are shown in table 3. The first dose of sublingual GTN (0.6 mg) while patients were on placebo produced a significant reduction in SBP and a rise in HR in the standing position within 2 minutes, and the effects persisted for 10 minutes (fig. 6). Compared with the first dose effect of GTN, the reduction in SBP was markedly attenuated both in the supine ($p < 0.05$) and standing ($p < 0.001$) positions when the same dose of GTN (0.6 mg) was administered while patients were taking 60 mg of ISDN every 6 hours (fig. 6). Effects of the first dose of GTN on SBP varied widely from one subject to another. The data for two representative patients are shown in figure 7, which shows that after the first dose of GTN, reduction in SBP was more marked in patient RS. However, when the second dose of GTN was given during regular ISDN therapy, the reduction in SBP was attenuated in both patients, even though plasma GTN levels were similar after the first and second dose of GTN (fig. 7).

Adverse Effects

None of the patients experienced any side effects after placebo therapy. Three patients had light-headedness associated with nausea in the upright position 1–2 hours after the first dose of ISDN (15 mg). Symptoms were associated with a SBP of 60 mm Hg or less but were relieved promptly when patients assumed the supine position. Postural hypotension and light-headedness did not recur with subsequent doses of ISDN. Six of the eight patients had moderately severe headaches after the first dose of ISDN, but these became less pronounced with higher doses of ISDN in two patients and remained unchanged in four.

Discussion

The results have shown that after the same dose of ISDN, plasma concentrations were significantly higher during sustained than during acute therapy. However, the depressive effect on arterial pressure was markedly attenuated during sustained therapy. After therapy with 15 mg of ISDN every 6 hours, the circulatory effects of this drug were markedly attenuated within 24–48 hours in all patients. Furthermore, continuous therapy with ISDN reduced the depressive effect on arterial blood pressure of 0.6 mg of sublingual GTN.

In animal experiments, the phenomenon of circulatory tolerance to nitrates has been extensively studied. A 10- to 50-fold shift in the blood pressure/dose-response curve to GTN after repeated intravenous or subcutaneous administration of GTN for 4–7 days has been produced in dogs, and rabbits and rats. The tolerance to the vasodepressor effects of GTN was dose- and time-related in rats. Furthermore, Rush and co-workers were able to produce a decrease in the vasodepressor response to GTN in dogs by infusing 1 mg/kg of GTN over a period of 1 hour. In animals, development of tolerance was not unique to GTN and a similar phenomenon has
been reported after repeated exposure to ethylene glycol dinitrate in rats and rabbits. Needleman and Johnson found that all nitrates induced tolerance to the circulatory effects of GTN: erythritol tetranitrate and mannitol hexanitrate induced the greatest tolerance, while ISDN induced the least tolerance.

In contrast to the reports in animals, observations of development of tolerance during nitrate therapy in man have been conflicting. The first report of circulatory tolerance to nitrates was described in 1888 in hypertensive patients who were receiving high doses of nitrates. In 1931, Crandell and co-workers reported that the repeated administration of erythrol tetranitrate, GTN, ethylene glycol dinitrate, methyl nitrate, and amyl nitrite led to the development of tolerance and cross-tolerance to the headache-producing action of these drugs. These workers did not provide information regarding the circulatory effects of these agents, but commented that the tolerance to the blood-pressure-lowering effects of these agents was not as easily established as was the tolerance to the headaches. Similarly, tolerance to headaches induced by nitroglycerin in industrial workers has also been well documented.

In a detailed study in 10 volunteers who were challenged with 0.3 mg sublingual GTN before and after daily therapy with pentaerythrol tetranitrate for 4 weeks, Schelling and Lasagna found that the reduction in blood pressure and increase in HR induced by GTN was markedly attenuated but not completely abolished after therapy with pentaerythrol tetranitrate. In the present study, the reduction in SBP

\[ \text{Figure 6. Cross-tolerance to the circulatory effects of glyceryl trinitrate (GTN) during therapy with isosorbide dinitrate (ISDN) every 6 hours (eight patients). Data represent mean } \pm \text{ SEM. The first dose of 0.6 mg of GTN given 6 hours after placebo produced a more marked reduction in systolic blood pressure (} p < 0.001) \text{ and a greater increase in heart rate (} p < 0.05) \text{ than the second dose of 0.6 mg of GTN given 6 hours after a dose of 60 mg of ISDN after daily (ISDN) therapy every 6 hours for 5 days.} \]
induced by GTN was also markedly attenuated after therapy with ISDN every 6 hours for 5 days (fig. 6). On the other hand, Aronow and colleagues were unable to show the development of circulatory tolerance to 0.3 mg GTN during sustained therapy with sublingual ISDN. This discrepancy can best be explained by the differences in protocols.

In the present study, the reduction in SBP induced by the first dose of 15 mg of ISDN was markedly attenuated after regular therapy with ISDN every 6 hours for 24–48 hours in all the patients. However, during sustained therapy, the circulatory tolerance was not complete and some reduction in SBP still occurred for up to 4 hours after the administration of single doses of ISDN (fig. 3). Thus, in the present study, acute oral administration of single doses of 15, 30, 60 and 120 mg of ISDN produced maximum reductions in SBP of 39, 42, 45 and 46 mm Hg, respectively, and the effects persisted for 6 hours. However, during sustained therapy with ISDN, the same single doses of 15, 30, 60 and 120 mg of ISDN produced maximum reductions in SBP of only 21, 21, 26 and 24 mm Hg, and the vasodepressor effects had disappeared by 6 hours. These results are somewhat different from those reported by Danahy and Aronow, who observed an average maximum reduction in SBP of 18 mm Hg 1 hour after acute therapy and 14 mm Hg after chronic therapy with the same dose; the effects on blood pressure persisted for 5 hours after both acute and sustained therapy.

High plasma ISDN concentration and significant pharmacologic effects after oral ingestion of ISDN in the present study are in contrast to reports by Needleman and colleagues, who could not demonstrate a vasodepressor response to nitrates administered orally or into the portal vein of rats. However, these workers and others have clearly shown that in animals, tolerance to the vasodepressor effects of nitrates administered intravenously or subcutaneously develops rapidly at the level of the vascular smooth muscle and is not due to the biotransformation of nitrates. Our results suggest a similar mechanism in man. Needleman and Johnson proposed that the circulatory tolerance to organic nitrates involves the oxidation of a critical sulphhydryl group in the "glyceryl trinitrate receptor." This hypothesis is supported by the reversal of in vivo and in vitro tolerance induced by the disulphide-reducing agent dithiothreitol.

The efficacy of nitrates in angina pectoris and heart failure is in part due to their ability to reduce arteriolar and venous tone, which in turn leads to a reduction in ventricular volume at rest and during exercise. However, the rapid development of partial tolerance to the depressive effect on SBP of ISDN during continuous therapy and cross-circulatory tolerance to GTN documented in the present and a previous report and attenuation of venodilator response to GTN during continuous therapy with ISDN is of some concern. The rapid hemodynamic and clinical tachyphylaxis to the afterload-reducing agent prazosin was recently reported in patients with heart failure. Theoretically, the therapeutic efficacy of nitrates would also be expected to diminish during chronic therapy if the peripheral effects of these agents were in any way related to their therapeutic effects. However, this has not been borne out in clinical practice, as the persistence of therapeutic efficacy of ISDN and GTN during continuous therapy with ISDN has been well documented in patients with angina pectoris and heart failure. Therefore, the peripheral effects of nitrates, although attenuated during chronic therapy, as shown in the present and previous reports, probably still play an important role in the maintenance of their therapeutic efficacy in angina pectoris and heart failure.

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U Thadani, D Manyari, J O Parker and H L Fung

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