THE DEVELOPMENT AND REVERSAL OF TOLERANCE TO ANTIANGINAL EFFECT OF ISOSORBIDE DINITRATE IN PATIENTS WITH EFFORT ANGINA

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The development and reversal of tolerance to the hemodynamic and anti-anginal effects of isosorbide dinitrate in a sustained release form (ISDN-SR) were investigated in 11 male patients (mean age 58.9 y.o.) with stable effort angina. Treadmill exercise test, evaluation of hemodynamic parameters and measurement of plasma ISDN concentrations were performed during the control period, on the 1st, 7th and 14th days of therapy with 40 mg of ISDN-SR orally every 8 h and, subsequently, on the day when ISDN-SR was re-administered after a 72 h placebo period (17th day).

Initially, exercise tolerance time (ETT) was prolonged significantly ($p < 0.001$) by ISDN-SR from 257 ± 50 sec in the control period to 434 ± 55 sec on day 1. This prolongation was significantly reduced with sustained therapy and ETT was shortened to 332 ± 69 sec on the 7th day ($p < 0.01$ vs day 1) and 326 ± 73 sec on the 14th day ($p < 0.01$ vs day 1). The effects of ISDN-SR initially observed were restored after a 72 h placebo period and ETT was prolonged to 432 ± 57 sec on the 17th day. The resting heart rate was increased significantly ($p < 0.01$ vs control) and systolic blood pressure was decreased ($p < 0.001$ vs control) by ISDN-SR on day 1. These changes were also diminished significantly ($p < 0.01$ vs day 1) with sustained therapy and were restored after a 72 h nitrate-free interval. The average plasma ISDN concentration was significantly higher during sustained than during acute therapy ($p < 0.01$).

It is concluded that partial tolerance to hemodynamic and antianginal effects developed during sustained (1 week) therapy with ISDN-SR and was reversed after a 72 h nitrate-free interval.

NITROGLYCERIN (NTG) was first used for the treatment of angina pectoris in the second half of the last century, and NTG and other organic nitrates continued to play an

important role in the treatment of ischemic heart disease.

Recently, nitrates have been widely used not only for the termination of angina attacks but also in prophylactic treatment of angina pectoris, in unloading therapy of congestive heart failure and for blood pressure control during various surgical procedures. The recent resurgence of

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Fig.1. Study protocol
ISDN-SR: isosorbide dinitrate in a sustained release form

interest in nitrate therapy has been related in part to the proliferation of delivery systems for organic nitrates^{1,2}. Prophylactic treatment of angina pectoris with long-acting NTG or isosorbide dinitrate (ISDN) preparations has become increasingly popular since the introduction of the 24-hour transcutaneous drug delivery system. Recently, there has been increasing utilization of intravenous NTG in acute myocardial infarction and for blood pressure control in acute cardiovascular emergencies or during various surgical procedures.

As these new forms of administration have become popular, however, reports from the clinical field indicate that nitrate administration designed to maintain therapeutic plasma levels for 24 hours leads to rapid development of tolerance^{3,4}. Although circulatory tolerance in terms of blood pressure and heart rate has been demonstrated⁵, antianginal and antiischemic tolerance in patients with effort angina has not been confirmed yet⁶⁻⁹. And, there has been no reports evaluating the serial changes in the degree of tolerance (diminution of drug effects) with repeat exercise tests.

In this study, we administered a sustained release form of ISDN (ISDN-SR) 40 mg 3 times daily for 2 weeks to patients with stable effort angina and evaluated the development and reversal of hemodynamic and antianginal tolerance to ISDN.

SUBJECTS AND METHODS

Study patients

Eleven male patients ranging in age from 44 to 68 years (average, 58.9) hospitalized for chronic, stable exertional angina pectoris were enrolled in this investigation. All patients had a positive

treadmill exercise test as defined by the development of chest pain during exercise with the appearance of ischemic ST segment depression (horizontal or downsloping ST segment depression ≥ 0.1 mV for at least 0.08 sec after the J point). Before entry into the study all patients performed at least two exercise tests and those with good reproducibility of results in the exercise tests were considered to be eligible for inclusion in the study. Selective coronary angiography demonstrated that every patient had significant coronary artery disease, defined as greater than 75% narrowing of the luminal diameter. Five patients had one-vessel, 3 patients had 2-vessel, and 3 patients had 3-vessel coronary artery disease.

Protocol

All antianginal medications other than sublingual ISDN were discontinued for at least 72 h before the study. ISDN-SR 40 mg was administered orally every 8 h (6:00, 14:00, 22:00) for 2 weeks and, subsequently, re-administered at 6:00 after a 72 h placebo period. Treadmill exercise test, evaluation of hemodynamic parameters and measurement of plasma ISDN concentrations were performed at 10:00 during the control period, on the first, 7th and 14th days of therapy with ISDN-SR and on the day when ISDN-SR was re-administered (Fig. 1). To evaluate the effects of sublingually administered ISDN during sustained oral ISDN-SR therapy, a treadmill exercise test was re-performed on the 14th day at 12:00, 10 min after sublingual ISDN (5 mg) administration in 3 patients in this study group.

The treadmill exercise test was performed in the fasting state according to the Bruce protocol. The patients were instructed to indicate the

TABLE I EXERCISE TOLERANCE TIME, TIME TO ONSET OF CHEST PAIN, TIME TO 1 mm ST DEPRESSION, AND DEGREE OF ST DEPRESSION WITH THE FIVE TREATMENT PERIODS

	control	day 1	day 7	day 14	day 17
ETT (sec)	257 ± 50	435 ± 55*	332 ± 69*†	326 ± 73*†	432 ± 57*
T ₁ (sec)	172 ± 45	339 ± 100*	249 ± 79*†	248 ± 53*†	343 ± 83*
T ₂ (sec)	185 ± 55	326 ± 91*	245 ± 56*†	242 ± 60*†	313 ± 80*
ST↓ (mm)	1.9 ± 0.4	0.7 ± 0.5*	1.0 ± 0.4*	1.2 ± 0.4*†	0.7 ± 0.5*

ETT: exercise tolerance time; T₁: time to onset of chest; T₂: time to onset of 1 mm ST depression; ST↓: degree of ST depression at identical exercise level

*: $p < 0.05$ compared with placebo; †: $p < 0.05$ compared with day 1

Fig.2. Individual data and mean ± standard deviation of exercise tolerance time after ISDN-SR during acute and sustained therapy. Exercise tolerance time was prolonged in all patients on day 1 but this prolongation was significantly reduced on the 7th and 14th days. After a 72 h placebo period, exercise tolerance time was prolonged again to the same level as on day 1.

point at which chest pain developed ("onset of chest pain") and exercise was terminated when the chest pain became moderate or, if angina did not occur, when the patient couldn't continue exercise because of fatigue. Angina of moderate severity was defined as chest pain of such severity that patient would normally stop activity and take sublingual NTG or ISDN. Three ECG leads (V₂, V₅, aV_F) were continuously monitored with an oscilloscope throughout the exercise test and a 12-lead ECG was recorded at rest, at 1-min intervals during exercise and for 5 min during recovery. The average values for heart rate and level of ST segment at 0.08 sec after the J point

were measured on a Marquette CASE XII exercise system at 1-min intervals. Blood pressure was also measured at 1-min intervals using a mercury sphygmomanometer. For assessment of the effect of nitrate, the following variables were measured and compared: (1) exercise tolerance time, (2) time to onset of chest pain, (3) time to 1 mm ST depression, (4) degree of ST depression at identical exercise level (same exercise duration as at the end point of control exercise test). If exercise did not induce any chest pain, nor significant ST depression after administration of ISDN, then maximal exercise duration (exercise tolerance time) was used instead of the time to

Fig.3. Serial changes in time to onset of chest pain and time to 1 mm ST depression. Values represent mean $\pm$ standard deviation. The time to onset of chest pain and time to 1 mm ST depression were significantly prolonged on day 1, but these initial effects were significantly attenuated on the 7th and 14th days and were restored after rechallenge following a 72 h placebo period.

* $p < 0.01$ compared with control

† $p < 0.01$ compared with day 1

onset of chest pain and the time to 1 mm ST depression.

Venous blood samples were obtained for determination of plasma ISDN, IS-2-MN and IS-5-MN concentrations just before each exercise test. The plasma drug concentrations were measured by gas chromatography.

Statistics

A paired sample Student *t*-test was used to compare the measurements during the 2 treatment periods. Probability (*P*) was considered significant at the $p < 0.05$ level. All values are expressed as mean $\pm$ one standard deviation.

RESULTS

Exercise testing variables (Table I)

(1) Exercise tolerance time (Fig. 2).

Initially, exercise tolerance time was prolonged in all patients from 257 ± 50 sec in the control period to 435 ± 55 sec on day 1 ($p < 0.001$). This prolongation was significantly reduced with sustained therapy and exercise tolerance time was shortened to 332 ± 69 sec on the 7th day ($p < 0.01$ vs day 1) and to 326 ± 73 sec on the

14th day ($p < 0.01$ vs day 1). After a 72 h placebo interval, exercise tolerance time was again prolonged to 432 ± 57 sec which is significantly ($p < 0.001$) longer than that on the 7th and 14th days.

(2) Time to onset of chest pain, and 1 mm ST depression (Fig. 3).

The length of time to onset of chest pain and 1 mm ST depression was significantly ($p < 0.01$) prolonged on day 1 from 172 ± 45 sec to 339 ± 100 sec and from 185 ± 55 sec to 326 ± 91 sec, respectively. These initial increases in the time to onset of chest pain and time to 1 mm ST depression were significantly reduced on the 7th and 14th days and were restored after rechallenge following a 72 h nitrate-free interval.

(3) Degree of ST depression at identical exercise levels (Fig. 4).

At identical exercise levels, the mean ST depression was significantly decreased from 1.9 ± 0.4 mm to 0.7 ± 0.5 mm on day 1. This change also was significantly diminished on the 7th day (1.0 ± 0.4 mm, $p < 0.05$ vs day 1) and the 14th day (1.2 ± 0.4 mm, $p < 0.05$ vs day 1) and

Fig.4. Individual data and mean $\pm$ standard deviation of degree of ST depression at identical exercise level. The degree of ST depression at identical exercise level was significantly decreased on day 1 and this change was diminished with sustained therapy.

Fig.5. Serial changes in hemodynamic parameters. Values represent mean $\pm$ standard deviation. The heart rate increased and systolic blood pressure decreased significantly on day 1. These changes were diminished with sustained therapy and restored after a nitrate-free interval.

SBP: systolic blood pressure

HR: heart rate

* $p < 0.01$ compared with control

† $p < 0.01$ compared with day 1

TABLE II PLASMA CONCENTRATION OF ISDN, IS-2-MN AND IS-5-MN WITH THE FOUR TREATMENT PERIODS

	day 1	day 7	day 14	day 17
ISDN (ng/ml)	6.7 ± 2	16.6 ± 5**	16.7 ± 4**	10.0 ± 5
IS-2-MN (ng/ml)	42.7 ± 21	68.8 ± 19**	67.4 ± 17*	39.8 ± 17
IS-5-MN (ng/ml)	152.0 ± 18	563.4 ± 137**	568.4 ± 100**	163.0 ± 29

ISDN: isosorbide dinitrate; IS-2-MN: isosorbide-2-mononitrate; IS-5-MN: isosorbide-5-mononitrate

*: $p < 0.05$, **: $p < 0.01$ compared with day 1

Fig.6. Plasma concentrations of ISDN, IS-2-MN and IS-5-MN. The average plasma ISDN, IS-2-MN and IS-5-MN concentrations were significantly higher during sustained than during acute therapy.

ISDN: isosorbide dinitrate

IS-2-MN: isosorbide-2-mononitrate

IS-5-MN: isosorbide-5-mononitrate

* $p < 0.05$,

** $p < 0.01$ compared with day 1

restored (0.7 ± 0.5 mm, NS vs day 1) after a nitrate-free interval.

Hemodynamic parameters (Fig. 5)

Mean resting heart rate increased from 65 ± 9 /min to 74 ± 9 /min ($p < 0.01$) and systolic blood pressure decreased from 128 ± 19 mmHg to 105 ± 9 mmHg ($p < 0.001$) after initial administration of ISDN-SR. These changes were significantly reduced with sustained therapy: heart rate decreased to 70 ± 7 /min on the 7th day ($p < 0.01$ vs day 1) and to 67 ± 9 /min on the 14th day

($p < 0.01$ vs day 1), systolic blood pressure increased to 117 ± 14 mmHg ($p < 0.01$ vs day 1) on the 7th day and 121 ± 12 mmHg ($p < 0.01$ vs day 1) on the 14th day. These attenuations of drug effects were restored after a 72 h nitrate-free interval; heart rate increased to 76 ± 10 /min (NS vs day 1) and systolic blood pressure decreased to 107 ± 10 mmHg (NS vs day 1) on the 17th day.

Plasma concentrations (Table II, Fig. 6)

During sustained therapy, plasma ISDN, IS-2-MN and IS-5-MN levels were substantially greater than those during the acute phases. The ratio of ISDN and metabolites showed no significant changes between acute and sustained phases.

The effects of sublingually administered ISDN during sustained therapy.

A typical patient who showed the development of tolerance with sustained nitrate therapy and the obvious effect of sublingual ISDN during sustained therapy in this study is shown in Fig. 7.

In the control period, patients had to stop exercise at 240 sec because of development of moderate chest pain and horizontal ST depression on the electrocardiogram. On day 1, after the initial dose of ISDN-SR, no chest pain and no ST depression were recognized at identical exercise levels (240 sec) and exercise tolerance time was prolonged to 480 sec. However, after 2 weeks of sustained therapy (on the 14th day), slight chest pain and ST depression developed at an identical exercise level and exercise tolerance time was shortened to 330 sec. Two hours after this exercise test on the 14th day, 5 mg of ISDN was administered sublingually and the exercise test was repeated. After sublingual ISDN, exercise tolerance time was markedly prolonged to 540 sec.

In 2 other patients, sublingually administered ISDN was effective; exercise tolerance time was

Fig.7. Case presentation

changed from 226 sec (control) to 470 sec (day 1), 240 sec (day 14) and 390 sec (after sublingual ISDN) in one patient and from 195 sec (control) to 495 sec (day 1), 270 sec (day 14) and 436 sec (after sublingual ISDN) in the other.

DISCUSSION

It has been known for many years that the vascular effects of organic nitrates are rapidly attenuated during sustained therapy. Thus, as previously stated, patients commonly have headaches during initial treatment with nitrates, but these usually disappear after a few days of continued therapy. Similarly, it has been shown in both animals^{10,11} and humans⁵ that the effects on systemic blood pressure and heart rate, observed during short-term therapy, are markedly attenuated during sustained treatment.

In a hemodynamic study, Parker et al⁵ analyzed the rate of development and reversal of tolerance to ISDN. After initial testing with sublingual ISDN 5 mg, patients were given ISDN 15 mg orally every 6 h. The response to sublingual ISDN was assessed before the morning dose of ISDN on the 2nd and again on the 3rd day. The patients were then put on placebo therapy and the hemodynamic effects of sublingual ISDN assessed on the fourth and 5th days. The study documented that the hemodynamic effects of sublingual ISDN were significantly modified on the 2nd day after the patients

had received only 3 doses of oral ISDN, i.e., 20 h after initial oral administration. On the 4th day of this study, 21 h after the last dose of oral ISDN, the response to sublingual ISDN was identical to that seen initially. Thus, this study indicates that tolerance to the hemodynamic effects of oral nitrates appears early and is rapidly reversed during a nitrate-free period.

Nitrate tolerance in angina pectoris

Danahy and Aronow⁶ and Lee et al⁷ failed to demonstrate a reduction in the antianginal effects of oral ISDN after 1 to 5 months of therapy with 120 to 160 mg given in 4 divided daily doses. Using single-blind, placebo-controlled, five-way crossover study, Schneider et al⁸ found a dose-related response in the frequency of anginal attacks, exercise ST segment changes, and exercise duration to angina following repeat oral ISDN dosing (5 to 80 mg every 4 h for 1 week). A more recent study from Schneider et al⁹ was unable to demonstrate any attenuation of nitrate effects after 1 month of therapy with 240 mg (6 × 40 mg) ISDN daily. This double blind, placebo-controlled protocol assessed angina attack rates and ST depression at a fixed work load with exercise testing on days 0, 7, and 28. Although hemodynamic tolerance occurred with respect to blood pressure responses to ISDN, no tolerance to anti-ischemic actions was demonstrable.

As mentioned above, several studies have

failed to demonstrate a diminution of the antianginal efficacy of nitrate, but well-designed recent studies have documented the presence of clinically important nitrate tolerance in patients given long-acting nitrates for a week or longer.

In a study of Thadani et al³ in which doses of 15, 30, 60 and 120 mg of ISDN were given acutely, there was a dose-dependent decrease in standing systolic pressure and an increase in heart rate at rest. Treadmill exercise testing documented an increase in exercise duration with each dose of ISDN, and the effect persisted for a period of at least 8 h. After 1 week of sustained therapy, there was a notable modification not only in hemodynamic effects, but more importantly in antianginal effects. The increase in exercise duration was dramatically less than during the short-term studies and the effect was apparent for only 2 h. These data clearly showed that nitrate tolerance to the antianginal effects of ISDN occurred within 1 week during sustained 4-times-daily therapy.

Recent studies have suggested that tolerance is more readily induced with large doses, frequent dosing regimens, and/or long acting formulations. In a double-blind, placebo-controlled study, Parker et al⁴ demonstrated that exercise duration was significantly prolonged at 2, 4 and 8 h, but not at 24 h, after the first application of transdermal ISDN (100 mg). After 7 to 10 days of daily dosing, exercise duration was similar for ISDN and placebo at 4, 8 and 24 h after application. This study concluded that transdermal ISDN in a dose of 100 mg is effective for 8 h during acute therapy, but that during sustained therapy, tolerance developed and no antianginal effects of ISDN persisted. Isosorbide-5-mono-nitrate is completely bioavailable and has a longer half-life than the parent compound. Once-a-day therapy with a slow-release formulation of IS-5-MN is used widely in Europe for 24-hour prophylaxis of angina pectoris. Thadani and coworkers¹² employed a slow-release preparation of IS-5-MN for short-term therapy and demonstrated an improvement in exercise time until the occurrence of angina pectoris after 4 h; however, at 20 and 24 h, there was no effect despite higher plasma concentrations. During subsequent sustained therapy (1 week), there was no difference in exercise tolerance after IS-5-MN and after placebo, suggesting the development of complete tolerance to the active agent.

In our study, the hemodynamic and antianginal effects of nitrate were obviously dimin-

ished with sustained therapy with ISDN-SR 40 mg 3 times daily, but no significant changes in effects were recognized between 1 week and 2 weeks of therapy. This fact suggested that nitrate tolerance to hemodynamic and antianginal effects developed within 1 week, but the degree of attenuation of effects showed no significant changes after that. We believe that nitrate tolerance is partial and not complete and that the effects of nitrate are markedly attenuated with sustained therapy but are partially maintained.

In an attempt to avoid the development of nitrate tolerance, investigators have examined the use of nitrate-free intervals. Schaer et al¹³ investigated the role of intermittent therapy with a transdermal nitroglycerin patch, using a daily nitrate-free interval (patches were worn only from 8 a.m. to 10 p.m.) in 13 patients with chronic stable angina. Since exercise tolerance was increased at 4 and 8 h after patch application during both acute and sustained therapy, they concluded that tolerance to the antianginal effects of the nitroglycerin patch can be avoided by providing a dosing regimen using interrupted exposure to nitroglycerin. Silber et al¹⁴ compared therapy with sustained-release ISDN (80 mg) given once with that given twice daily for 2 weeks. During once-daily therapy, the effects on exercise-induced ST-segment depression and simultaneously recorded left ventricular ejection fraction were maintained. But during twice-daily therapy, there was a substantial diminution in the antianginal effects of the medication. In a double-blind, placebo-controlled trial, Rudolph et al¹⁵ demonstrated the attenuation of ISDN's effect on ST depression at a fixed bicycle load after therapy with 40 mg of ISDN q.i.d. for 2 weeks, but no such loss of effect was evident at a dosage of 20 mg b.i.d. in a separate group of patients. Parker et al¹⁶ investigated the effects of different dosage schedules of oral ISDN. In this placebo-controlled trial, patients were treated with oral ISDN administered either 2, 3 or 4 times daily. During treatment with 2 and 3 times daily administration, treadmill walking time was longer throughout the 5-hour testing period than during the placebo phase. In contrast, during treatment with 4 times daily administration, treadmill walking time was prolonged at 1 h but not at 3 and 5 h after the last dose. Thus, it would appear that dosage schedules designed to provide a washout period are helpful in the prevention of

nitrate tolerance. Recently, Parker et al¹⁷ compared the antianginal effects of buccal nitroglycerin (3 mg) 3 times daily with oral isosorbide dinitrate (30 mg) 4 times daily. Isosorbide dinitrate produced a dramatic increase in treadmill walking time during the 5-hour study period after the initial dose, but after 2 weeks of therapy, the improvement in exercise time after the morning dose persisted for only an hour. In contrast, buccal nitroglycerin improved walking time throughout the 5-hour study period during both short-term and sustained therapy. This study indicates that nitrate tolerance is preventable by using less frequent dosing, a shorter-acting nitrate, or both.

What are the possible reasons for the controversial results with antianginal tolerance to nitrate? The use of different nitrate compounds, the total daily dose, the kind of exercise test performed and the duration of therapy cannot account for the controversial results. And a strict placebo-controlled randomized double-blind crossover study protocol is not the key answer for the interpretation of the conflicting results, because no tolerance development was seen in some studies.⁹ We believe that one of the most uncertain points in interpreting presently available studies is the absence of documentation of patients' compliance. Since the development of nitrate tolerance is rapid and its reversal is also rapid, patients' compliance with dose ingestion is pivotal in the development of tolerance. Simple methods for documentation of patients' compliance, such as tablet counting, or a diary for daily recording of ingestion, are not very reliable and can therefore be of only supportive value. So we enrolled only hospitalized patients in this study and confirmed that the patients took all their medications consistently.

Recently, the development of tolerance has also been demonstrated in patients with congestive heart failure¹⁸⁻²¹ and in human coronary arteries *in vivo*.²² It is apparent that nitrate tolerance is a clinically relevant problem. To avoid tolerance, physicians should attempt to use the least amount of nitrate that achieves the desired clinical effect. Smaller doses, less frequent dosing, and relatively short acting compounds should be employed, or with longer-acting preparations therapy should be interrupted for part of each 24-hour period — one should attempt to achieve a nitrate-free interval that lasts at least 10 h. In this study, the development of tolerance was evident when 40 mg

of ISDN-SR was given 3 times a day. The development of tolerance can be avoided or minimized when 20 mg of ISDN-SR 3 times a day, 40 mg of ISDN-SR twice a day and/or conventional ISDN is given.

Mechanisms of nitrate tolerance

The mechanisms of nitrate tolerance have not been fully clarified. The demonstration of increased plasma ISDN levels during sustained therapy in this and previous studies^{3,4} indicates that pharmacokinetic tolerance, which is characterized by a reduction in the concentration of the drug at the site of action caused by an alteration of absorption, metabolism, or excretion, can be excluded for the nitrate. Cumulative data from a number of studies²³⁻²⁷ support the hypothesis that long-term nitrate therapy somehow depletes the reduced sulfhydryl groups necessary for the conversion of the nitrate molecule into an active vasodilating molecule (S-nitrosothiol). If complete depletion of sulfhydryl groups had developed, then the activity of sublingually administered NTG or ISDN after chronic nitrate therapy would also be lost. But, our study and previous data²⁸ have suggested that sublingually administered NTG or ISDN are effective, even in the presence of nitrate tolerance. These findings would suggest that the mechanism of tolerance is not fully explained by the theory of depletion of sulfhydryl groups alone. Therefore, a different or additional mechanism is required to explain the development of tolerance.

Vasodilators are known to induce significant neurohormonal responses.^{29,30} Thus, it has been shown that nitroprusside infusion is associated with increased plasma renin activity and catecholamine levels.³¹ These vasoactive substances may attenuate or modify the effects of vasodilators and, conceivably, could play a role in the development of tolerance. In regard to nitrate, Packer et al²¹ reported that continuous therapy with intravenous nitroglycerin for 48 h was accompanied by increases in plasma renin activity, and this change was paralleled by the development of hemodynamic tolerance.

It has also been suggested that alterations in plasma volume may develop with nitrate administration. Lis and coworkers³² have reported that the venous hematocrit was diminished during NTG infusions. It is possible that expanded plasma volume during sustained nitrate therapy may be, in part, responsible for the diminished

hemodynamic and antianginal effects.³³

The attenuation of effects of nitrates is probably a result of the development of true tolerance to the drug, activation of counteractive vasoconstriction forces and volume expansion. These mechanisms may be operative to varying degrees in different parts of the circulation and in different patients.

CONCLUSIONS

It is apparent that during short periods (within 1 week) of regular oral administration of sustained release isosorbide dinitrate 40 mg 3 times a day, the hemodynamic and antianginal effects are greatly reduced. Physicians should try to maintain more patients on "as needed" nitrate therapy rather than sustained long-acting therapy to avoid the induction of nitrate tolerance.

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