Randomized Study to Evaluate the Relation Between Oral Isosorbide Dinitrate Dosing Interval and the Development of Early Tolerance to Its Effect on Left Ventricular Filling Pressure in Patients With Chronic Heart Failure

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Background. Early development of nitrate tolerance has been shown in patients with chronic congestive heart failure (CHF) receiving continuous nitroglycerin therapy. The influence of dosing interval of oral isosorbide dinitrate (ISDN), the nitrate preparation most widely used for the treatment of CHF, has not been investigated.

Methods and Results. We performed a prospective, randomized study to evaluate the effect of various regimens of oral ISDN on the development of early tolerance to its effect on left ventricular filling pressure in patients with moderate to severe CHF. Forty-four responders (20% or greater reduction in mean pulmonary artery wedge pressure lasting 1 hour or longer) were divided into four groups of 11 patients each, and randomized to receive their effective ISDN dose (40–120 mg) Q 4 hours, Q 6 hours, Q 8 hours, or t.i.d. (drug given at 0, 6, 12, and 24 hours allowing 12 hours of ISDN washout interval between the third and fourth doses). All groups demonstrated a significant and comparable reduction in LV filling pressure following administration of the first ISDN dose. Early attenuation of hemodynamic response was demonstrated with frequent dosing (Q 4 hours and Q 6 hours) ISDN. Tolerance was prevented with a Q 8-hour regimen as demonstrated by preserved hemodynamic response to each dose. The effect of each dose, however, was short-term, with return of pulmonary artery wedge pressure to baseline level at 2 to 4 hours, resulting in an intermittent effect totaling no longer than 12 hours of the 30-hour study period. The use of a t.i.d. regimen resulted in marked attenuation of response after the third dose with complete restoration of nitrate effect following a 12-hour washout period between the third and fourth doses. ISDN plasma concentration was measured in five patients in each of the Q 4- and Q 8-hour groups. In the Q 4-hour group, plasma levels were significantly higher after administration of the last dose than after the first dose (area under the curve, 242±216 versus 123±130 ng/ml, p<0.05), and trough levels before administration of the second and the fifth dose (15±17 and 27±27 ng/ml, respectively) were both markedly higher than the baseline value of 2±4 ng/ml.

Conclusions. Our data demonstrate the development of tolerance and early attenuation of effect on left ventricular filling pressure with frequent oral dosing (Q 4 and Q 6 hours) with ISDN in patients with chronic CHF, which may be related to persistently elevated trough blood levels of ISDN. The development of tolerance can be reversed after a washout period of 12 hours and can be prevented with a Q 8-hour administration. These regimens, however, are limited by an inconsistent effect. Although long-term implications of these findings need further evaluation, the present study demonstrates the difficulty of maintaining a persistent ISDN-mediated reduction in left ventricular filling pressure in patients with chronic, moderate to severe CHF. These results suggest the need to use intermittent ISDN therapy allowing a daily nitrate washout interval and the rationale for combined vasodilator therapy in patients with CHF. (Circulation 1991;84:2040–2048)
The use of organic nitrates has demonstrated great promise in the treatment of both acute and chronic congestive heart failure (CHF). The drugs have been reported to exert a favorable hemodynamic effect, to enhance exercise capacity, and in combination with the arterial dilator hydralazine, possibly to improve survival in patients with mild to moderate CHF. Recent information, however, has suggested that the efficacy of nitrate therapy may be severely limited by early development of tolerance leading to a marked attenuation of its initial hemodynamic effect. Several investigations have demonstrated rapid development of tolerance to nitrate when administered continuously either intravenously or topically. This phenomenon seems to be preventable by intermittent therapy with periodic discontinuation of drug administration to allow relatively long nitrate washout periods. Oral isosorbide dinitrate (ISDN) is the nitrate preparation most widely used in the treatment of chronic CHF. There is, however, no information available regarding the development of tolerance with this form of therapy in patients with CHF and the optimal regimen required to prevent its occurrence. Therefore, the purpose of the present study was to evaluate the effects of various dosing regimens of oral ISDN on the development of tolerance to its initial hemodynamic effect in an attempt to form a rational basis to the dosing intervals of this drug in the treatment of patients with CHF.

Methods

Study Patients

Seventy-one patients with chronic CHF due to left ventricular (LV) systolic dysfunction who were admitted with worsening symptoms entered the study. Twenty-seven patients were excluded from the study or data analysis for the following reasons: lack of hemodynamic response (17 patients), increasing symptoms during baseline (three patients) or during the study (one patient), incomplete or technically inadequate data (four patients), development of psychosis (one patient), or transient ischemic attack (one patient) during the study. Forty-four patients responded to ISDN therapy and completed the study. There were 32 men and 12 women ranging in age from 23 to 83 years (mean±SD, 53±13 years). The cause of CHF was suspected to be coronary artery disease in seven patients and dilated cardiomyopathy in 37 patients. Of the patients with dilated cardiomyopathy, a past history of hypertension was obtained in 12 patients, of excessive alcohol consumption in 12 patients, of both in four patients, and of peripartum cardiomyopathy in one patient. No patient had primary valvular disease or clinical evidence of active myocardial ischemia at the time of the study. All patients were classified on admission in the New York Heart Association functional classes III or IV but were in stable clinical and hemodynamic condition at the time of the study. The diagnosis of LV systolic dysfunction was confirmed by contrast or radionuclide ventriculography in 35 patients and demonstrated LV ejection fraction ranging from 8% to 39% (mean, 22±7%). In the remaining nine patients, LV systolic dysfunction was confirmed by echocardiography.

Hemodynamic Measurements and Computations

Right heart catheterization was performed with a balloon-tipped, triple-lumen Swan-Ganz catheter. Pressures in the right atrium and pulmonary artery and LV filling pressure, determined indirectly from the mean pulmonary arteriolar wedge pressure (PAWP), were recorded on Electronics for Medicine VR-12 or AR-6 recorders; mean pressures were obtained by electronic integration. Heart rate was determined from the electrocardiographic recording, and arterial blood pressure was measured by the standard cuff method. Cardiac output was determined by thermodilution as previously described. Calculations of mean arterial blood pressure, cardiac index, stroke volume index, systemic vascular resistance, and pulmonary vascular resistance were performed by standard formulas. Serum levels of ISDN were determined by gas–liquid chromatography.

Study Protocol

After the patients were clinically stabilized, right heart catheterization was performed at least 16 hours before the onset of the study to guard against previously reported spontaneous hemodynamic changes after the procedure. All forms of organic nitrates and other long-acting vasodilators were withheld for at least 24 hours. Prestudy doses of digitalis and diuretic therapy were continued throughout the study period. On the day of the study, baseline hemodynamic measurements were taken every 30 minutes to achieve two consecutive measurements with less than 10% variation. The values determined at the last measurement were used as baseline data. All patients were then given 40 mg of oral ISDN, and repeat hemodynamic measurements were obtained hourly for 4 hours. Hemodynamic response to ISDN was defined as a 20% or greater decrease in PAWP sustained for 1 hour or more (two consecutive measurements). The definition of response was based on a previously reported coefficient of variation of 17% in serial measurements over 24 hours in a group of patients with chronic CHF and similar hemodynamic profile treated with placebo. In responders to 40 mg ISDN, hemodynamic measurements were repeated every 1–2 hours for 30 hours. In nonresponders to this dose, a washout period of 24 hours or longer was allowed, and 120 mg ISDN was then administered following an identical protocol. Nonresponders to

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120 mg ISDN were excluded from the study. Responders to ISDN at any dose used were prospectively randomized to four groups of 11 patients each and received their effective dose in one of the following four drug regimens: 1) Q 4 hours; 2) Q 6 hours; 3) Q 8 hours; and 4) t.i.d. when drug was given at 0, 6, 12, and 24 hours, allowing a 12-hour interval between the third and fourth doses. Venous blood was obtained in a sample of five patients following the first and the last dose in both the Q 4-hour (every hour) and the Q 8-hour (every hour for 4 hours and then at 8 hours) groups for determination of serum ISDN level.

Statistical Analysis

All data comparisons between the four groups studied were made by analysis of variance. The changes in LV filling pressure within each group were analyzed by analysis of variance for repeated measurements and the Newman-Keuls tests. Comparisons of ISDN serum concentration in the same patients were made by a Student's paired t test and between groups by a nonpaired t test.

Analysis was performed with the CLINFO system and the SAS statistical package on the IBM 370 system at the University of Southern California. All values were expressed as mean±1 SD. A value of p<0.05 was considered statistically significant.

Results

Comparison of Baseline Clinical and Hemodynamic Data

Mean baseline values for the clinical and hemodynamic data for all four groups are shown in Table 1. No significant difference existed between the four groups with regard to age, gender, mean effective ISDN dose, LV ejection fraction, and all measured and calculated baseline hemodynamic variables.

Hemodynamic Response to ISDN Given Q 4 Hours

LV filling pressure was reduced significantly from 27±7 to 19±8 mm Hg at 2 hours (p<0.05) (Figure 1). Values remained significantly lower than baseline at 4 and 6 hours (20±8 and 20±7 mm Hg, respectively). However, values at 8 hours after initiation of therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Q 4 hours</th>
<th>Q 6 hours</th>
<th>Q 8 hours</th>
<th>t.i.d.</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
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<td>49±19</td>
<td>56±8</td>
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<td>ISDN dose (mg)</td>
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<tr>
<td>EF (%)</td>
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<td>21±6</td>
<td>20±2</td>
<td>NS</td>
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<tr>
<td>HR (beats/min)</td>
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<td>95±20</td>
<td>88±15</td>
<td>96±12</td>
<td>NS</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
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<td>98±11</td>
<td>102±14</td>
<td>97±14</td>
<td>NS</td>
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<tr>
<td>CI (l/min/m²)</td>
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<td>2.3±0.6</td>
<td>2.1±0.5</td>
<td>1.9±0.5</td>
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</tr>
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<td>SVI (ml/m²)</td>
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<td>25±10</td>
<td>24±8</td>
<td>20±5</td>
<td>NS</td>
</tr>
<tr>
<td>RA (mm Hg)</td>
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<td>11±7</td>
<td>13±5</td>
<td>NS</td>
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<tr>
<td>PAWP (mm Hg)</td>
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<td>27±8</td>
<td>26±5</td>
<td>24±6</td>
<td>NS</td>
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<tr>
<td>SVR (dyne-seclcm⁻³)</td>
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<td>1,650±341</td>
<td>1,995±620</td>
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<td>NS</td>
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<tr>
<td>PVR (dyne-seclcm⁻³)</td>
<td>280±107</td>
<td>274±182</td>
<td>353±189</td>
<td>225±77</td>
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ISDN, isosorbide dinitrate; EF, ejection fraction; HR, heart rate; MBP, mean blood pressure; CI, cardiac index; SVI, stroke volume index; RA, mean right atrial pressure; PAWP, mean pulmonary artery wedge pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

FIGURE 1. Effect of 40–120 mg of oral isosorbide dinitrate (ISDN) given Q 4 hours on mean pulmonary artery wedge pressure (PAWP) in 11 patients with chronic congestive heart failure. Closed circles, p<0.05 vs. baseline (BL). Shaded area represents values equal to or lower than baseline value minus one coefficient of variation (CV) in baseline values repeatedly measured over 24 hours in a similar patient population treated with placebo.5
and for the remainder of the 30-hour study monitoring period were not statistically different from baseline.

Response to ISDN Given Q 6 Hours

The administration of the first dose resulted in a significant fall in PAWP from 28±8 to 19±7 mm Hg after 1 hour (Figure 2). The following doses resulted in either no effect (dose 2) or attenuated effect (doses 3 and 5). Most values obtained after 6 hours of therapy were not statistically different from baseline (hours 8, 10, 12, 18, 20, 22, 24, 28, and 30).

Response to ISDN Given Q 8 Hours

The administration of the first dose resulted in maximum reduction in PAWP from 26±5 to 17±4 mm Hg at 2 hours (p<0.05) (Figure 3). The administration of each dose given in intervals of 8 hours resulted in a significant fall in PAWP, reaching its peak at 2 hours (second dose, 18±6 mm Hg; third dose, 19±6 mm Hg; fourth dose, 17±7 mm Hg; all p<0.05). However, the effect was lost between 2 and 4 hours after drug administration, resulting in insignificant difference from baseline at 4, 6, 8, 12, 14, 16, 20, 22, 24, 28, and 30 hours. Thus, Q 8-hour daily administration resulted in a significant reduction in PAWP for no longer than 12 hours of the 30-hour study period.

Response to ISDN Given t.i.d.

The first dose resulted in a significant fall in PAWP from 24±6 to 15±7 mm Hg at 1 hour and lasting for 4 hours (17±5 mm Hg) (Figure 4). The second dose of ISDN given 6 hours later demonstrated slightly attenuated effect, with values significantly lower than baseline at 2 hours (16±6 mm Hg) but not at 4 hours (18±5 mm Hg, p=NS). The administration of the third dose of ISDN was followed by markedly attenuated reduction of PAWP to 19±5 mm Hg at both 2 and 4 hours; these values were not statistically different from baseline values. In contrast, the administration of the fourth dose of ISDN following 12 hours of washout time resulted in complete restoration of the initial hemodynamic effect.

Figure 5 compares the recorded value of PAWP at baseline and 1, 2, 4, and 6 hours after the first and the last doses of ISDN given 24 hours after the initiation of the study. Marked attenuation of the initial effect...
is seen after 24 hours of therapy with the drug given Q 4 hours and Q 6 hours. This attenuation is prevented with a Q 8-hour regimen and overcome by a 12-hour washout period during the night.

**ISDN Plasma Levels**

Measured values of plasma ISDN concentration after the first and last doses in the Q 4- and Q 8-hour groups are shown in Figure 6. The area under the curve as measured over 4 hours after the first dose in the Q 4-hour group was 123±130 ng/ml and increased significantly to 242±216 ng/ml (p<0.05) after the last dose. Trough levels before administration of the second dose (15±17 ng/ml) and the seventh and last doses (23±21 ng/ml) were markedly elevated in each patient compared with baseline values (2±4 ng/ml). These differences, however, did not reach statistical significance because of the limited number of patients.

The area under the ISDN serum concentration curve following the first dose in the Q 8-hour group was similar to that seen in the Q 4-hour group at 122±87 ng/ml (p=NS) and was increased after the last dose to 168±121 ng/ml. This increase was smaller than that seen in the Q 4-hour group (27% versus 49%) and achieved only borderline statistical significance (p=0.083). Trough levels were 3±3 ng/ml before administration of the second dose and 6±7 ng/ml before administration of the last dose (both p=NS versus baseline).

**Discussion**

The development of tolerance to organic nitrates was first described almost a century ago and has been repeatedly reported since, both in animal experiments and in patients with cardiovascular disease. Although the clinical significance of this phenomenon has often been doubted, more recent information has clearly shown that nitrates tolerance may severely limit the benefit of this therapy in patients with cardiovascular diseases.

Several investigations in patients with CHF have demonstrated early development of tolerance to the hemodynamic effects of nitrates when administered continuously either by the intravenous or transdermal route. These studies, in addition to in vitro experiments demonstrating development of toler-
ance to the nitrate-mediated vasodilatory effect following prolonged preincubation with nitroglycerin, suggest that continuous, uninterrupted exposure to organic nitrates is associated with early attenuation of response to these drugs. The present study is the first attempt to evaluate, in a prospective randomized trial, the continuous efficacy of oral ISDN, the most commonly used nitrate preparation in patients with chronic CHF. Our findings demonstrate early development of tolerance with marked attenuation of effect on LV filling pressure with frequent dosing (Q 4 and Q 6 hours) of the drug. These results are comparable to previously reported data demonstrating attenuation of hemodynamic effects, occurring within the first several hours of therapy, with continuous administration of nitroglycerin in a similar patient population.8–11

Evaluation of ISDN plasma concentration in the Q 4-hour group demonstrates that attenuation of hemodynamic effect occurs despite gradual accumulation and significantly higher plasma levels of the drug. These findings help to exclude a reduction in drug availability as a cause for attenuated effect and support the development of drug tolerance as a mechanism for attenuated response. Similar findings were reported by Thadani et al,21 who showed rapid development of tolerance to the hemodynamic and anti-ischemic effects of ISDN given every 6 hours in patients with angina pectoris despite higher ISDN plasma levels during sustained therapy. Higher plasma ISDN concentrations after 24 hours of therapy may be explained by accumulation of the drug when given every 4 hours, as indicated by gradually increasing trough levels and by its previously described nonmonoeponential elimination phases.22,23

A relation between duration of a continuous, uninterrupted exposure to organic nitrates and the magnitude of tolerance development to their effect has been clearly demonstrated in in vitro experiments.20 This relation is further supported by our results, which demonstrate a development of early tolerance to frequent ISDN dosing but a persistent hemodynamic effect with the use of longer (8-hour) interdose intervals, allowing a return of ISDN plasma concentration to near baseline levels after each dose. Failure to show early tolerance development with an ISDN regimen of Q 8 hours in this study supports previous reports demonstrating prevention of nitrate tolerance with the use of “nitrate-free” intervals in patients with CHF. Packer et al6 demonstrated tolerance development to the hemodynamic effect of intravenous nitroglycerin occurring within 48 hours of therapy in the majority of their studied patients. These investigators were able to prevent the development of tolerance with intermittent administration using a 12-hours-on, 12-hours-off regimen. Similarly, Sharpe et al12 were able to prevent nitrate tolerance with the use of intermittent transdermal nitroglycerin therapy with a daily patch-off interval of 8 hours. In addition, a relation between oral ISDN interdose interval and the development of tolerance as shown in the present study was demonstrated by Parker et al24 in patients with angina pectoris. These investigators demonstrated tolerance to the anti-ischemic effects of 30 mg ISDN given orally four times daily and its prevention with a twice or three times daily regimen.

Our findings also demonstrate a reversal of tolerance developed with frequent dosing of oral ISDN and complete restoration of the initial hemodynamic effect after drug withdrawal of 12 hours. Similar results were demonstrated by Parker et al,25 who studied the rate of development and reversal of tolerance to the circulatory response of ISDN in patients with stable angina and showed reversal of nitrate tolerance occurring within 21 hours after discontinuation of therapy.

Although the use of ISDN Q 8 hours seems to prevent early development of tolerance in the present study, a significant reduction of LV filling pressure was seen for a cumulative time of no longer than 6–10 hours per day because of the relatively short-term effect of each dose and return to predrug values between doses. Although duration of ISDN effect varied between individual patients and even between the groups studied, similar results have been re-
ported recently by Bassan,26 who found less than 3 hours’ duration of anti-ischemic effect of each oral ISDN dose and no more than 6 hours of antianginal benefit during a 24-hour period when the drug was given three times daily.

Seventeen patients were excluded from the present study because of lack of hemodynamic response to 120 mg of ISDN. Such resistance to high doses of ISDN has been reported by us to occur in approximately 25% of patients with chronic CHF.27 Lack of hemodynamic response to the drug is seen mostly in patients with elevated right atrial pressure and may be an additional limitation of nitrate therapy in this patient population. The mechanisms of resistance to ISDN are not entirely clear and require further investigation.

There are several potential limitations to the present study. First, the results of this evaluation are limited to the effect of ISDN on resting LV filling pressure measured in the supine position. It is possible that this may not correlate with the effect of this drug on other important clinical parameters such as exercise capacity, quality of life, and survival. More research is obviously needed to evaluate the relation between the development of tolerance to acute hemodynamic response demonstrated in the present study and chronic clinical effects of ISDN given at various drug regimens. Despite this potential limitation, a reduction of LV filling pressure has been shown to be a sensitive and consistent indicator for nitrate effect in patients with CHF.5 This change is clearly related to symptomatic improvement of dyspnea, most probably a result of reduction of dyspnea-causing stimuli shown to be mediated by mechanoreceptors within the pulmonary circulation.28 In addition, reduction of resting LV filling pressure has been shown to indicate similar changes during both dynamic and isometric exercise.29,30 A possible association between reduction in pulmonary pressures and enhancement of exercise capacity may be suggested by the relation between an increase in right ventricular ejection fraction and exercise capacity and by the fact that only vasodilator agents producing venodilation, and thus reducing PAWP, have been shown to improve exercise capacity in patients with chronic CHF.31 Leier et al2 demonstrated improvement of exercise capacity following 3 months of ISDN therapy given Q 6 hours in patients with CHF. Such an improvement may be explained by residual reduction in PAWP, albeit not statistically significant in our study. It is also possible that the mild residual reduction in resting PAWP may be enhanced during upright exercise29 leading to improvement. Further studies evaluating the effect of nitrate tolerance on hemodynamic profile during exercise in the upright position are obviously needed for further understanding of the potential benefits of nitrates in patients with CHF.

Additional limitation is related to variations between patients in magnitude and timing of tolerance development.5,11 Such variations suggest that the results of the present study cannot be applicable for each individual patient with chronic CHF. Individual differences in the development of nitrate tolerance, however, have been shown to be unpredictable by clinical or hemodynamic data available to the clinician.11

Another potential limitation of this study may be related to its relatively short duration (30 hours) and the high dose of ISDN used. These two factors are particularly important considering previously shown relations between dose of nitrates and duration of exposure to these drugs and the magnitude of tolerance development to their vasodilatory effect.19,20 A longer follow-up may therefore demonstrate a higher degree of tolerance, while a smaller ISDN dose may result in a lesser incidence of tolerance in patients with chronic CHF.

What is the ideal regimen of oral ISDN in patients with chronic CHF? The results of this study clearly demonstrate the difficulty of maintaining a lasting hemodynamic effect for 24 hours with oral ISDN therapy either because of early development of tolerance with frequent dosing or because of long periods of disappearing drug effect with interdose intervals of a Q 8-hour regimen. A frequent dosing of oral ISDN is associated with development of tolerance within several hours of initiation of therapy, which could limit the efficacy of such therapy when given continuously. However, administration of two or three doses of the drug every 4–6 hours results in significant hemodynamic improvement lasting 6–12 hours and may be adequate for symptomatic relief throughout periods of maximum activity or symptoms when combined with a daily 12 hours of nitrate washout period to allow restoration of full efficacy.

Our findings demonstrate a potential limitation of oral ISDN when used as monotherapy and the rationale for combined therapy in patients with chronic CHF. Such a clinical rationale may be supported by the beneficial effect of combined therapy of ISDN and hydralazine on survival in patients with mild to moderate CHF3 and by recent preliminary data32 demonstrating added hemodynamic efficacy of ISDN in patients with chronic CHF already treated with angiotensin-converting enzyme inhibitors. Such a combination therapy may enhance hemodynamic effect during a period of anticipated maximum symptoms and help to maintain a more favorable hemodynamic profile during long nitrate interdose intervals or washout periods.

Substantial hemodynamic fluctuations with oral ISDN given Q 8 hours may be preventable with the use of longer-acting nitrate preparation. Such an assumption is supported by previous studies demonstrating persistent hemodynamic effect lasting for at least 10–12 hours with the use of transdermal nitroglycerin11 and a recent report by Sharpe et al12 demonstrating long-term efficacy of transdermal nitroglycerin given intermittently allowing a daily 8-hour “nitrate-free” interval.
Summary

The present study compared in a prospective, randomized fashion the persistence of hemodynamic response to oral ISDN as manifested by its effect on LV filling pressure in four groups of responders (11 patients in each group) with moderate to severe chronic CHF randomized to receive the drug Q 4 hours, Q 6 hours, Q 8 hours, or t.i.d. (at 0, 6, 12, and 24 hours). The outcome of this study indicates early development of tolerance to the initial effect on LV filling pressure with frequent dosing (Q 4 hours and Q 6 hours, which may be related to persistently elevated ISDN trough plasma levels. Tolerance was reversed with complete restoration of hemodynamic effect after a washout period of 12 hours. ISDN Q 8 hours seemed to prevent early development of tolerance; however, this regimen resulted in only intermittent hemodynamic effect with significant reduction in LV filling pressure for only 12 hours or less of the 30-hour study duration. These results demonstrate the difficulty of achieving a continuous reduction in LV filling pressure with oral ISDN either because of early development of tolerance seen with frequent administration or because of inconsistent effect as a result of long interdose intervals. Further evaluation is needed before the implications of these findings on long-term efficacy of the drug can be fully understood. However, the results of this study point out the limitation of continuous administration of frequent dosing of oral ISDN and suggest the need for intermittent therapy allowing a daily nitrate washout interval and the rationale for combined vasodilator therapy in patients with CHF in order to prevent hemodynamic worsening during long nitrate-washout or interdose intervals.

Acknowledgments

We thank the nurses in the Intensive Cardiac Unit, LAC and USC Medical Center, and Laura Weber, RN, for their assistance in the performance of this study. We also thank Alice Madrid for her excellent secretarial work.

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**KEY WORDS** • nitrates • vasodilators • clinical trials • pulmonary artery wedge pressure
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Circulation. 1991;84:2040-2048
doi: 10.1161/01.CIR.84.5.2040

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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