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Double-Blind, Placebo-Controlled Study to Evaluate the Effect of Organic Nitrates in Patients With Chronic Heart Failure Treated With Angiotensin-Converting Enzyme Inhibition

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Background**—**Organic nitrates are widely used in the treatment of chronic heart failure (CHF). No information, however, is available regarding their effect in patients already treated with ACE inhibitors.

Methods and Results**—**In a randomized, double-blind, crossover design, we studied the effects of high-dose (50 to 100 mg) transdermal nitroglycerin (NTG) and placebo given daily for 12 hours in 29 patients with CHF (NYHA functional classes II to III). Exercise time (4 hours after patch application) showed a progressive improvement during NTG administration, with an increase of 38 ± 35 seconds ($9\pm7\%$) at the end of the first month (P=NS), 76 ± 28 seconds ($16\pm6\%$) at the end of the second month ($P=0.01$), and 117 ± 34 seconds ($27\pm6\%$) at the end of the third month ($P=0.003$). No significant change was seen during placebo administration (12 ± 20, 5 ± 26, and 19 ± 28 seconds, all P=NS). Exercise time 8 hours after NTG application measured at 3 months was also significantly longer, with a difference of 87 ± 28 seconds ($P=0.006$), but not with placebo (23 ± 36 seconds, $P=0.53$). Assessment of quality of life and need for additional diuretics or hospitalizations for CHF failed to demonstrate a significant difference between the 2 treatment periods. In contrast, NTG decreased left ventricular end-diastolic ($-2.1\pm0.1\%$, $P<0.05$) and end-systolic ($-3.2\pm1.3\%$, $P<0.05$) dimensions and augmented LV fractional shortening ($24.7\pm10.5\%$, $P<0.03$). The effect of placebo on these parameters was not statistically significant.

Conclusion**—**High-dose nitrate therapy significantly improves exercise tolerance and left ventricular size and systolic function in patients with chronic, mild to moderate CHF already treated with ACE inhibitors. These findings support the role of organic nitrates as an adjunctive therapy to ACE inhibitors in patients with chronic CHF. **(*Circulation*. 1999;99:2652-2657.)**

Key Words: heart failure ■ nitroglycerin ■ angiotensin ■ enzymes

Recent clinical trials demonstrate a widespread use of organic nitrates in patients with chronic heart failure (CHF).[1–3] The clinical rationale for their use is based on their beneficial effect on hemodynamic profile,[4] myocardial ischemia,[5] magnitude of mitral regurgitation,[6] endothelial function,[6,7] cardiac remodeling,[8] and exercise capacity.[9,10] In addition, when combined with hydralazine, nitrates improved maximum oxygen consumption, left ventricular (LV) ejection fraction (EF), and survival.[11,12] No information, however, is available regarding the effect of chronic nitrate therapy in patients already treated with ACE inhibitors. Because ACE inhibitors have become the cornerstone of drug therapy for CHF, reevaluation of nitrate effect in patients already treated with these drugs is of important clinical relevance. The present study was therefore designed to evaluate, in a randomized, placebo-controlled fashion, primarily the effects of nitrate therapy on treadmill exercise time and secondarily its effects on the incidence of symptomatic worsening requiring hospitalization and/or additional diuretics, quality of life, and LV dimensions in patients with CHF who are treated with standard heart failure therapy, including ACE inhibitors.

Methods

Study Population

This single-center study was performed at the Los Angeles County/University of Southern California Medical Center. The inclusion criteria were ambulatory men and women, ≥18 years old, with a history of CHF due to either coronary artery disease or idiopathic dilated cardiomyopathy, who were symptomatic despite therapy with digitalis, diuretics, and ACE inhibitors, in NYHA functional classes II and III, with LVEF <40% and exercise duration on the Modified Naughton protocol between 3 and 13 minutes. Exclusion criteria included obstructive or restrictive cardiomyopathy; pericardial con-

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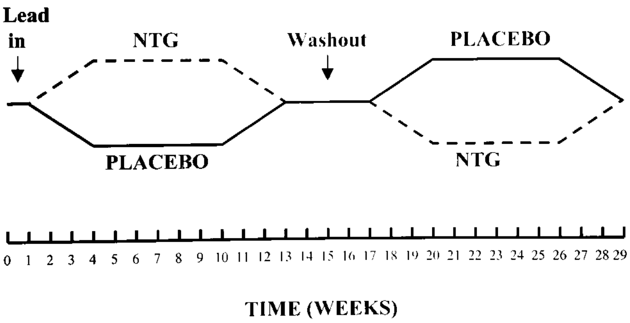

Figure 1. Study design included a single-blind placebo stabilization period of 1 week and 2 periods of 12 weeks each in which patients were randomized and crossed over to receive transdermal NTG 50 to 100 mg for 12 h/d or transdermal placebo. The 2 treatment periods were separated by 4 weeks of a single-blind placebo washout period.

striction; acute myocardial infarction within the previous month; angina pectoris; treadmill exercise limited by ischemia; primary lung disease; intermittent claudication or motor disability; fixed heart rate (pacemaker); major disorders of the hematological, hepatic, renal, immunological, central nervous, or endocrine systems; women of childbearing potential not using adequate contraception; and pregnant or nursing mothers.

Number of Patients

The study was planned to include a total of 20 evaluable patients who completed the 2 double-blind evaluation periods. Patients who dropped out for any reason before completion of the protocol were to be replaced.

Study Protocol

The study was designed as a double-blind, randomized, placebo-controlled, crossover trial and was divided into 5 phases (Figure 1): Phase I was a single-blind, placebo run-in period lasting 1 week. After signing an informed consent form, patients gave a complete medical history and had a physical examination, laboratory evaluation plus a chest radiograph, and LVEF assessment if not done in the previous 3 months. The first set of 2 placebo patches was applied at the hospital. Phase II was a single-blind period lasting 2 to 5 weeks. During this phase, patients continued to wear 2 placebo patches and had a practice exercise treadmill test (ETT), followed by up to 5 qualifying ETTs starting 1 week later 4 hours after patch application and repeated 5 to 9 days apart to achieve 2 reproducible exercise times lasting between 3 and 13 minutes. After the qualifying ETT, a repeat ETT was performed 4 hours later, at 8 hours after patch application, to evaluate the duration of effect. Phase III was a double-blind period "A" lasting for 12 weeks. After the qualifying ETT, patients were randomized to a double-blind regimen of either 2 placebo patches or a placebo patch and a 2-mg/h nitroglycerin (NTG) patch for 3 to 7 days and then 2 patches of NTG. Patients were supervised 2 hours after initial drug application and drug uptitration. Follow-up during this double-blind treatment phase included physical and laboratory examinations, 12-lead ECG, and ETT every 4 weeks. Phase IV was a 4-week±5-day washout single-blind, placebo period, followed by a second baseline ETT, which was repeated 4±3 days later and then up to 3 times if duration of exercise differed from the qualifying ETT by >45 seconds. At the qualifying visit or the last visit, a complete evaluation, including physical and laboratory examinations and a 12-lead ECG, were repeated, followed by randomization to double-blind period "B". Phase V was a 12-week, double-blind period B. Patients were crossed over to receive the other regimen of either placebo or NTG. The protocol for period B was identical to that used for period A.

Study Procedures

Exercise time was the primary prespecified efficacy measure. Patients had to be on constant doses of diuretics, digitalis, and ACE inhibitors for ≥5 days before each exercise test; not use tobacco products or consume alcohol within 8 hours; and fast for ≥2 hours before ETT. Time of day, room temperature, and personnel supervising the test were kept constant. ETT was performed at 4 hours after the application of study patches. To evaluate duration of therapy, a second ETT at 8 hours was performed at the qualifying visit, before initiation of either therapy, and at the end of 3 months of treatment. A modified Naughton protocol was used, with workload increased every 2 minutes, as follows: 1.5 mph/0% grade, 2 mph/0% grade, 2 mph/3.5% grade, 2 mph/7% grade, 2.5 mph/7% grade, 3 mph/7.5% grade, 3 mph/10% grade, 3 mph/12.5% grade, 3 mph/15% grade, and 3.4 mph/14% grade.

Quality of life was assessed by use of the Living with Heart Failure questionnaire,[13] which was administered in the patient's native language before ETT and other clinical assessments.

An M-mode echocardiogram was used for the assessment of intracavitary LV dimensions before initiation of treatment and at 3 months. LV end-diastolic dimension (LVEDD) was measured at the R wave of the ECG from the leading edge of the left side of the interventricular septum and the posterior endocardium echo. The LV end-systolic dimension (LVESD) was measured at the peak downward motion of the interventricular septum.[14] LV fractional shortening was calculated as follows: FS=LVEDD−LVESD÷LVEDD×100. All measurements were performed by a blinded observer.

Data Analysis

ANOVA for repeated measures was used to exclude a significant interaction between groups A (patients receiving NTG as first drug) and B (patients receiving placebo as first drug) with treatment or time to determine permissibility to evaluate the 2 groups together. An unpaired *t* test and a Fisher exact test were used to compare demographic data between groups A and B. An ANOVA for repeated measures and Newman-Keuls tests were used to determine a statistical difference between the absolute values as well as difference from baseline in treadmill exercise time and quality of life. A Fisher exact test was used to determine difference in number of hospitalizations for all causes, hospitalization for CHF, increase in diuretic dose, and total CHF episodes. To exclude any carryover effect related to the crossover design of the study,[15] a separate analysis was performed for change in exercise time during NTG treatment given as a first therapy in group A patients and during placebo given as the first treatment in group B patients.

The following parameters were analyzed: (1) treadmill exercise time to exhaustion, 4 hours after patch application at baseline and monthly for 3 months during therapy; (2) treadmill exercise time 8 hours after patch application at baseline and at the end of 3 months of treatment; (3) standing values of heart rate and systemic blood pressure immediately before ETT; (4) symptomatic worsening requiring hospitalization or a temporary increase in diuretics [because initial diuretic dosage was maintained at a constant level during the study, a single dose of intravenous furosemide or oral hydrochlorothiazide (50 mg) or metolazone (5 mg) QD for 3 days was given to treat episodes of CHF worsening]; (5) quality of life; (6) LVESD and LVEDD and fractional shortening; and (7) side effects.

Because enhancement of exercise performance with other vasodilators required several weeks of therapy,[16,17] change in exercise time was analyzed in patients who completed the study. In addition, the conservative approach of the carry-forward method recently used in other trials[16,17] was also used for assessment of changes in exercise time and quality of life. Changes in LV dimensions and fractional shortening were analyzed in all patients who completed ≥1 treatment arm. A 2-tailed Student's *t* test was used to compare changes from baselines.

Analyses were performed by the Statistical Consultation and Research Center at the University of Southern California School of Medicine using the CLINFO system and the SAS statistical package on the IBM 370 system. Values were given as mean±SEM. A probability value of <0.05 was considered statistically significant.

Results

Fifty-one patients entered the phase 1, run-in period. Twenty-two patients were excluded before randomization for the

TABLE 1. Baseline Variables in the 2 Study Groups

Parameter	Group A (n=14)	Group B (n=15)	*P*
Age, y	48±3	48±4	0.87
Male, %	72	93	0.17
CHF duration, y	2.1±0.65	1.1±0.27	0.18
LVEF, %	24±3	26±2	0.61
Captopril dose, mg/d	106±20	88±11	0.38
Lasix dose, mg/d	80±13	103±22	0.38
Digoxin dose, mg/d	0.22±0.08	0.24±0.03	0.37
NTG dose, mg/d	54±5	59±4	0.84

Group A includes patients receiving NTG as first drug; group B, patients receiving placebo as first drug.

following reasons: treadmill exercise duration >13 minutes, 11 patients; LVEF >40%, 4 patients; worsening CHF, 2 patients; death, 2 patients; and protocol violation, 3 patients. Twenty-nine patients met the inclusion criteria and were randomized into the trial. There were 24 men and 5 women with a history of CHF for 1.5±0.3 years. Age ranged between 24 and 68 years, with a mean of 48±2 years. LVEF was between 11% and 41%, with a mean of 25±2%. The cause of CHF was suspected to be coronary heart disease in 7 and unknown in 22 patients. Of the patients with idiopathic cardiomyopathy, a history of excessive alcohol consumption was obtained in 3 patients, hypertension in 1 patient, and myocarditis in 1 patient. No patient had primary valvular disease or clinical evidence of active myocardial ischemia on randomization. Twelve patients were in NYHA functional class II, and 17 were in class III. All patients were treated with captopril and furosemide with mean doses of 89±13 and 99±11 mg, respectively. Twenty-eight patients were treated with digoxin at a mean dose of 0.232±0.011 mg.

Baseline Comparisons Between Treatment Groups

Fourteen patients were randomized first to NTG (group A) and 15 to placebo (group B). Table 1 provides demographic information, baseline clinical characteristics, and dose of medications for the 2 groups. No significant differences were found between the 2 groups.

Effect of Treatment on Exercise Time

Figure 2 demonstrates changes in exercise time during the study obtained 4 hours after patch application in 20 patients

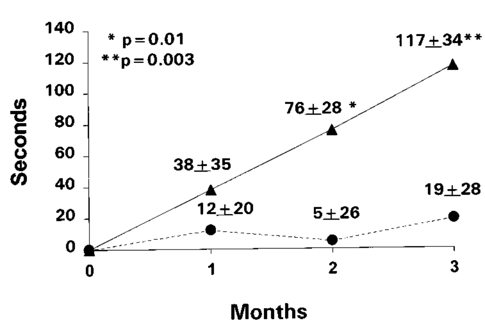

Figure 2. Change in treadmill exercise time from baseline 4 hours after administration of NTG (▲) and placebo (●).

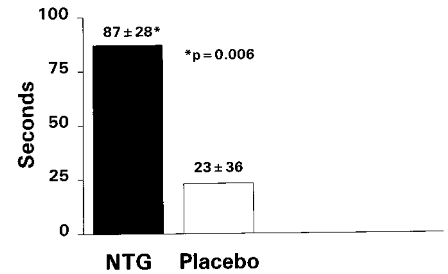

Figure 3. Change in treadmill exercise time from baseline 8 hours after patch application at end of 3 months of treatment with NTG and placebo.

who completed the study. Exercise time increased progressively during NTG treatment, with 38±35 seconds (9±7%) at the end of the first month (*P*=NS), 76±28 seconds (16±6%) at the end of the second month (*P*=0.01), and 117±34 seconds (27±6%) at the end of the third month (*P*=0.003). In contrast, no significant change was demonstrated during the placebo treatment period [12±20, 5±26, and 19±28 seconds, respectively].

Changes in exercise time at 8 hours after 3 months of treatment are shown in Figure 3. NTG treatment increased exercise time 87±28 seconds compared with baseline (*P*=0.006), whereas placebo resulted in a 23±36-second reduction (*P*=0.53).

By the carry-forward method, the effect of NTG was evaluated in 28 patients and that of placebo in 23 patients. The increase of treadmill exercise time on NTG was 13±29 seconds at 1 month (*P*=0.65), 59±22 seconds at 2 months (*P*=0.01), and 83±30 seconds at 3 months (*P*=0.01). The effect of placebo was not significant (1±20 seconds at 1 month, −2±24 seconds at 2 months, and 10±26 seconds at 3 months).

Subgroup Analysis of Exercise Time

To detect any carryover effect due to the crossover design of the study, a separate analysis was performed for the 2 subgroups of 10 patients receiving either NTG or placebo as the first treatment (Figure 4). NTG (group A) resulted in an increase in treadmill exercise time of 39±45 seconds at month 1 (*P*=0.41), 87±29 seconds at month 2 (*P*<0.02), and 120±31 seconds at month 3 (*P*<0.04). In contrast, use of placebo as the first drug (group B) resulted in an 18±9-

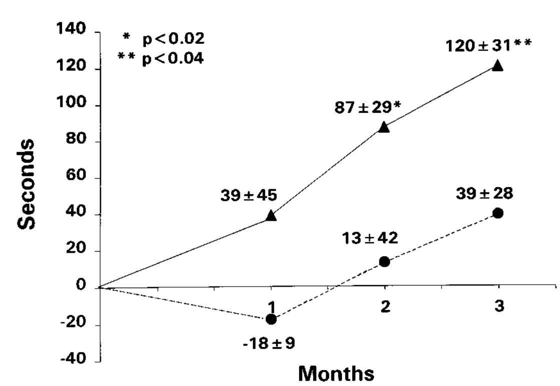

Figure 4. Change in treadmill exercise time from baseline in patients who received NTG as first drug (▲) and patients who received placebo as first drug (●).

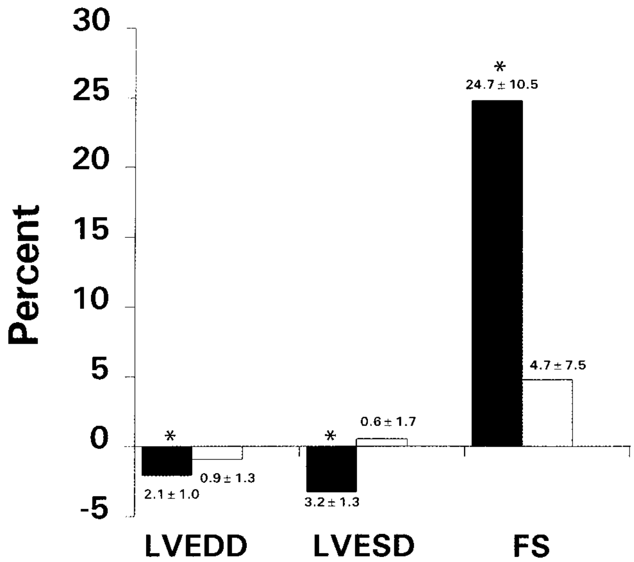

Figure 5. Percent change in LVEDD, LVESD, and fractional shortening (FS) from baseline after 3 months of therapy with NTG (solid bars) and placebo (open bars). *Statistically significant.

second decrease in month 1, a 13±42-second increase in month 2, and a 39±28-second increase in month 3. Changes with placebo were not statistically significant.

Heart Rate and Blood Pressure

No difference was demonstrated in heart rate or blood pressure during either NTG or placebo treatment. Heart rate was 92±4 and 90±3 bpm at baseline before initiation of NTG and placebo, respectively, and was 96±3 and 93±4 bpm at the end of 3 months of therapy. Blood pressure was 114±3/79±2 and 110±3/76±3 mm Hg at baseline before initiation of NTG and placebo, respectively, and 113±3/77±2 and 111±3/75±2 mm Hg after 3 months of therapy.

Echocardiographic Measurements

Twenty-four patients had echocardiographic data at baseline and then at 3 months after NTG therapy, placebo treatment, or both (Figure 5). The change in LVEDD in 18 patients after NTG was −1.6±0.6 mm, or −2.1±1.0% ($P<0.05$), and −0.6±0.9 mm, or −0.9±1.3%, with placebo in 19 patients ($P=0.51$). LVESD was reduced 2.1±0.7 mm, or 3.2±1.3%, with NTG ($P<0.05$) and increased 0.1±0.8 mm, or 0.6±1.7%, with placebo ($P=0.74$). Fractional shortening showed an absolute increase of 2.1±0.1% or a relative increase of 24.7±10.5% with NTG ($P<0.03$), in contrast to 0% or 4.7±7.5%, respectively, with placebo ($P=0.54$).

Quality of Life

Quality-of-life score was 60±6 at baseline before NTG (22 patients) and 55±6 before placebo (25 patients, $P=0.6$) and showed a slight decrease during the treatment with both NTG and placebo (Figure 6). The changes, however, were not statistically significant.

Hospitalizations and Need for Additional Diuretics

Six of 26 patients (23%) were hospitalized during NTG therapy, 5 of these for worsening CHF (Table 2). In comparison, 5 of 27 patients (19%) were admitted during placebo therapy, 3 due to worsening CHF. Six patients required additional doses of diuretics in both groups. The total numbers of worsening CHF episodes were 11 during NTG treatment and 9 during placebo treatment. All these differences between the 2 regimens did not reach statistical significance.

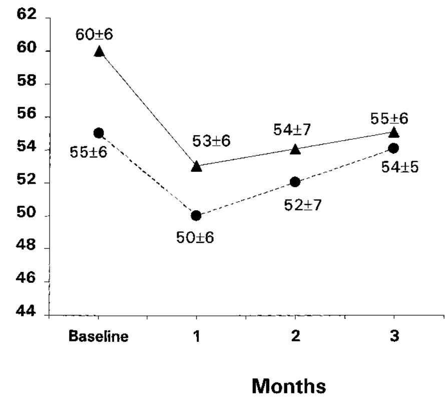

Figure 6. Values of total quality of life score at baseline and monthly during therapy with NTG (▲) and placebo (●). There were no statistically significant changes in quality of life in the 2 groups.

Other Side Effects

The most common adverse effect during NTG treatment was irritation at the site of patch application (15 patients versus 1 during placebo) and headache (12 patients versus 0 during placebo). The study was discontinued prematurely during NTG treatment in 6 patients (23%), during placebo in 3 patients (11%), and during the washout period in 1 patient (3%). Reasons for premature discontinuation of NTG were worsening of CHF (1 patient), stroke (1 patient), headache (3 patients), and noncompliance with the protocol (1 patient). Placebo was discontinued prematurely because of sudden death (1 patient), acute myocardial infarction (1 patient), and noncompliance with study protocol (1 patient). One patient was discontinued during the washout period because of noncompliance with the protocol.

Discussion

Effect on Exercise Capacity

Decreased exercise capacity is one of the clinical hallmarks of chronic CHF and an important therapeutic target. The present study demonstrates a significant and progressive prolongation of treadmill exercise time induced by nitrates. A significant improvement in exercise tolerance was demonstrated as early as 2

TABLE 2. Episodes of Hospitalization and Increase in Diuretics for Worsening of CHF

Treatment	Hospitalization for All Causes	Hospitalization for CHF	Increase in Diuretic Dose	Total CHF Episodes
NTG (n=26)	6	5	6	11
Placebo (n=27)	5	3	6	9

No significant difference was found in all parameters listed between the 2 groups.

months after initiation of treatment, with a maximum increase of nearly 30% at 3 months and an effect lasting for at least 8 hours after NTG application. These findings support the results of 2 early studies that evaluated, in a randomized, double-blind fashion, the effect of oral isosorbide dinitrate (ISDN) given for 3 months on either maximal exercise tolerance[9] or oxygen consumption in CHF patients not receiving ACE inhibitors.[10] Further evidence for nitrate-mediated improvement in exercise capacity was provided by the V-HeFT studies,[11,12,18] which demonstrated an improvement in peak oxygen consumption mediated by ISDN/hydralazine used in combination. The results of the present study, therefore, indicate that the previously demonstrated effect of nitrates on exercise capacity is maintained when the drug is used in CHF patients already treated with ACE inhibitors.

A possible explanation for the observed effect on exercise tolerance may be multifactorial, including reduction in right and left ventricular filling pressures, pulmonary hypertension, and myocardial ischemia.[19,20] In addition, nitrate-mediated improvement of endothelial dysfunction[21] may result in improved arterial compliance and therefore may lead to improved exercise capacity.

Effect on Symptoms and Quality of Life

No difference was noted in quality of life or need for additional diuretics and hospitalizations for worsening of heart failure. Although these findings may be related to the limited number of patients studied, other investigators have also reported a lack of relationship between change in exercise tolerance, symptoms, and quality of life.[22,23] At the same time, however, nitrate therapy resulted in a progressive increase in exercise time in this study, reaching significance only at 2 months and achieving maximum effect at 3 months. Thus, the study period may not have been long enough to separate the effect of NTG on quality of life and symptoms from that of placebo. An additional cause for the discrepancy between effect on exercise tolerance and quality of life score may be related to the use of maximal exercise time in this study. Although this parameter is valuable in grading CHF severity and prognosis,[24] submaximal exercise may provide a better measure for the clinical status of patients with CHF.[25] Submaximal testing, however, is less objective in assessing exercise capacity and has only marginal value in predicting prognosis, especially in patients with less than severe CHF.[26] Assessment of maximal and submaximal exercise capacity therefore seems to provide somewhat different information and may be complementary.[25]

Effect on LV Remodeling

Transdermal NTG therapy for 3 months resulted in a small but significant reduction in both LVEDD and LVESD and a substantial improvement in LV systolic function. These findings are supported by previous data demonstrating nitrate-mediated prevention of chronic LV remodeling after myocardial infarction both in animals and in humans[27,28] and are similar to the improvement in LVEF demonstrated in the V-HeFT studies with nitrates and hydralazine without ACE inhibitors.[18] The present study extends the result of the V-HeFT trials and demonstrates a favorable effect of nitrates on LV size and function even when they are added to ACE inhibitors.

Rationale for Selecting NTG Regimen

In this study, an intermittent, high-dose nitrate regimen was used. Several investigators have clearly demonstrated that intermittent administration with a daily nitrate washout interval is an effective method for the prevention of nitrate tolerance seen with continuous nitrate administration.[4,29] Prevention of nitrate tolerance has recently also been shown with a concomitant administration of antioxidants such as hydralazine[30] and vitamins C[31] and E.[32] More data, however, will be needed to establish the longer-term effect of these drug combinations. The use of relatively high-dose NTG was based on our previous experience indicating the need to use high doses of nitrate given either orally[4,33] or transdermally[34,35] to achieve an effective hemodynamic response in patients with chronic CHF.

Side Effects

The most common side effects of NTG were irritation at the site of patch application and headache. The latter was seen in almost half of the patients and resulted in discontinuation of therapy in ≈10%. The incidence of headache in this study was higher than that reported in other studies[11,12] and was probably related to the use of high-dose NTG.

Study Limitations

The present study may be limited by the relatively small number of patients included. This limitation is somewhat minimized by the crossover design, which can produce statistically and clinically valid results with far fewer patients than would otherwise be required.[15] A crossover design, however, is not free of limitations, especially those related to a potential carryover effect. In this study, a washout period of 1 month was used to allow time for the effect of NTG to dissipate before the administration of placebo. Furthermore, a separate analysis of change in exercise time during treatment with NTG and placebo, when given first, revealed similar results and confirmed the validity of the overall study findings. The effect of dropouts and missing data points are problems for any study, but their effect may be enhanced in a study with crossover design.[15] For that reason, exercise data were analyzed in 2 different ways: first, only in patients who completed the study, excluding patients with missing values, and second, with a carry-forward approach. Both analyses provided similar results, indicating a significant and progressive increase in exercise tolerance during NTG treatment.

In the present study, the effect of NTG on exercise time was evaluated at 4 and 8 hours after the administration of the drug. It is therefore not clear whether the effect of the drug was sustained during the patch-free interval. In addition, the patients included in this study reflect the heart failure population in our medical center, which differs somewhat from older patient populations with a higher incidence of coronary artery disease reported in other CHF trials. Because of the relatively small number of patients, it was not possible to separately analyze the effects of organic nitrates on different subgroups of patients.

Summary

The present study compared, in a prospective, randomized, and double-blind fashion, the effect of 3 months of therapy with high-dose intermittent NTG and placebo on exercise tolerance, quality of life, worsening of CHF episodes, and echocardiographically measured LV dimensions in patients with chronic CHF already treated with standard therapy. The results showed a significant, progressive and long-acting enhancement of treadmill exercise time starting after 2 months of therapy and reaching a maximum increase of nearly 30% at 3 months. In addition, use of nitrates led to a significant reduction in LV size and augmentation of systolic function. The results of this study support the use of organic nitrates for enhancement of exercise tolerance and improvement of LV function in patients with mild to moderate CHF (NYHA functional classes II and III) who are already being treated with standard CHF therapy, including ACE inhibitors.

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