Comparative Hemodynamic Effects of Chewable Isosorbide Dinitrate and Nitroglycerin in Patients with Congestive Heart Failure

By Esteban Mikulic, M.D., Joseph A. Franciosa, M.D., and Jay N. Cohn, M.D.

SUMMARY
Vasodilators are known to be effective in improving the hemodynamics of congestive heart failure by increasing cardiac output and reducing left ventricular filling pressure (LVFP). Long-acting agents are needed to augment the practicality and availability of chronic vasodilator therapy. In the present study the vascular effects of chewable isosorbide dinitrate (CHIS), sublingual nitroglycerin (NTG) and placebo (P) were compared in eight patients with high LVFP due to heart failure. Patients with LVFP (pulmonary wedge pressure) over 14 mm Hg were given CHIS, 10 mg, NTG, 0.6 mg, and P, two chewable tablets, in random fashion. Heart rate (HR), blood pressure (BP), and LVFP were monitored for three hours after each drug. HR was not significantly affected by any drug, although it rose slightly after NTG and fell after CHIS. Significant reduction of BP occurred only after NTG, with peak effect at five minutes, but lasting only 15 minutes. NTG reduced LVFP 5.1 mm Hg (19.5%, \( P < 0.05 \)), at peak effect, but LVFP was no longer significantly lower by 20 minutes after NTG. After CHIS, LVFP fell significantly within five minutes, reached a peak reduction of 8.6 mm Hg (32.7%, \( P < 0.01 \)) at 15 minutes, and remained significantly lower through three hours. Thus CHIS provides a nitrateraction of rapid onset and sustained effect that may be useful for chronic vasodilator therapy of heart failure.

Several investigators have recently shown that reduction of impedance to left ventricular ejection improves the hemodynamics of left ventricular failure. Vasodilators consistently reduce left ventricular filling pressure (LVFP) and increase cardiac output with only modest decreases in arterial pressure. Beneficial results have been reported in acute left ventricular failure associated with hypertension or acute myocardial infarction as well as chronic refractory heart failure due to ischemic or primary myocardial failure and mitral insufficiency. In the majority of these studies short-acting intravenously administered agents, such as sodium nitroprusside or phentolamine, have been used and have required invasive hemodynamic monitoring to carefully titrate dosage.

The intravenously administered impedance reducing agents are generally more potent and are preferred in severely ill patients requiring acute treatment. In many of these patients who improve or in other less severely ill patients it may be desirable to continue vasodilator therapy, thus giving rise to a need for effective, long-acting vasodilators. Sublingual nitroglycerin (NTG) has been shown to mimic, at least qualitatively, some of the effects of nitroprusside in left ventricular failure complicating acute myocardial infarction, although its effects on cardiac output are variable. The duration of action of NTG is short-lived making it impractical for use as a chronic vasodilator agent; however, longer acting nitrates might be useful. Sublingual isosorbide dinitrate has been shown to decrease LVFP for one hour which still seems too short to be of practical value.

We have previously reported successful chronic vasodilator therapy in a patient who was treated with various agents including oral isosorbide dinitrate. This experience prompted us to study the effects of oral isosorbide dinitrate in patients with heart failure and we found that this agent, given as a 20 mg oral dose, reduced LVFP for over four hours. Although these findings strongly suggested that isosorbide dinitrate given by mouth is absorbed, skepticism based on earlier animal studies may still exist, especially regarding individual patients' responses. Isosorbide dinitrate is also available in a chewable tablet form which is absorbed largely by the oral mucosa. The onset of action of chewable isosorbide dinitrate (CHIS) is similar to sublingual NTG, but its duration is longer. Thus, CHIS might be
preferred as a long-acting nitrate in those situations where absorption of the oral form is questionable. The present study was therefore undertaken to evaluate the hemodynamic effects of CHIS in patients with heart failure.

Methods

Studies were performed in eight patients with evidence of congestive heart failure (dyspnea, S₃ gallop, jugular venous distention, edema, and pulmonary congestion on physical or radiological examination) secondary to ischemic or primary myocardial disease or acute myocardial infarction. The diagnosis of primary myocardial disease was made in patients with a history of marked alcohol abuse and/or a lack of evidence to support any other etiology of their heart disease. Ischemic myocardial disease was diagnosed if previous myocardial infarction could be documented by typical history, serial electrocardiographic and serum enzyme changes. Patients with other forms of heart disease were excluded. Patients with acute myocardial infarction were included since we observed no significant difference between them and chronic heart failure patients in responsiveness to nitrites in our previous studies.

The eight subjects, seven males and one female, averaged 55.4 years of age. One patient had acute myocardial infarction and one had ischemic myocardiopathy. The other six all were thought to have primary myocardial disease; of these, two had normal coronary arteriograms at cardiac catheterization, three gave a history of alcohol abuse, and one had no apparent cause for heart failure. All patients had class III failure (New York Heart Association classification) at the time of study and all except the one with acute myocardial infarction were receiving maintenance digitalis therapy up to the time of study. No one had evidence of acute pulmonary edema or cardiogenic shock, and no side effects or complications occurred during the study period.

All studies were performed at the patient’s bedside or in a special procedure room adjacent to the coronary care unit. On the day of study all diuretics, vasodilators, and antianginal medications were withheld, but patients receiving maintenance digitalis therapy were given their daily dose prior to study. Prior antianginal medications consisted of thiazide diuretics only in two patients.

After obtaining written informed consent, right heart catheterization was performed using a Swan-Ganz flow-directed balloon tipped catheter inserted percutaneously via an antecubital, femoral, or internal jugular vein. The catheter was connected to a P23D Statham pressure transducer. Zero reference level was at the mid-axillary line with the patient supine; all pressures were recorded in this position on a Hewlett Packard recorder. Heart rate (HR) was measured from the electrocardiogram; systemic arterial blood pressure (BP) was measured directly from a brachial artery cannula in three patients, and indirectly by the standard cuff technique in the other five patients.

Occluded pulmonary arterial pressure or pulmonary arterial diastolic pressure was taken as LVFP. If control LVFP averaged 15 mm Hg or higher on three successive readings at 5 minute intervals, the patient was given either 10 mg CHIS, 0.6 mg NTG sublingually, or placebo (P). LVFP, HR, and BP were recorded every 5 minutes for the first half hour and every 15 minutes for the next 2.5 hours. After the first 3-hour period if LVFP was 15 mm Hg or higher the second drug was given and measurements repeated in the same manner for 3 more hours. At the end of the second 3-hour period if LVFP was 15 mm Hg or higher, the third drug was given and monitoring carried out in the same manner. The dosage and duration of observations were based on previously reported data.

In two of the three patients in whom arterial pressure was measured directly, cardiac output was also measured in duplicate by the dye dilution technique injecting indocyanine green into the pulmonary artery and sampling from the brachial artery. Measurements were made just before each drug administration, and once after each drug when peak effect on LVFP was observed.

The order of drug administration was randomized in double blind fashion and the randomization code was not broken until the study was completed and all data calculated. The double-blind applied only to CHIS and NTG which were identical in appearance. The investigator knew when NTG was being given because of its different appearance.

Statistical analysis of the data was performed by means of Student’s t-test.

Results

Control values for LVFP, HR, and BP prior to each drug administration are shown in Table 1. None of the differences between pre-P, pre-CHIS, and pre-NTG

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Control Hemodynamics Before Each Drug Administration</th>
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<tbody>
<tr>
<td>Patient no.</td>
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<td>1</td>
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<td>25</td>
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<tr>
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Abbreviations: LVFP = left ventricular filling pressure (mm Hg); BP = systemic arterial blood pressure (mm Hg); HR = heart rate (beats/min); P = placebo; CHIS = chewable isosorbide dinitrate; NTG = nitroglycerin.
values were statistically significant for any parameter measured, suggesting that there was no carry-over effect from previous drug administrations. Only one patient did not receive all three drugs; the pulmonary artery catheter became displaced in patient 2 at the end of the second drug period and could not be repositioned resulting in failure to administer NTG to this patient.

The mean values for changes in HR are plotted in figure 1. None of the changes were statistically significant in any group compared to control time 0, but HR tended to increase after NTG, decrease after CHIS, and remain the same with P. When the groups were compared to each other, neither NTG nor CHIS differed from P, but NTG gave HR significantly higher than CHIS (P < 0.05) between 20 and 180 minutes after drug.

Systolic and diastolic BP changed significantly only following NTG (fig. 2). Peak reduction in systolic pressure after NTG occurred at 5 minutes, while significant reduction was no longer seen at 15 minutes. Diastolic BP was also down maximally 5 minutes after NTG, and was still significantly lower at 20 minutes but no longer so from 30 minutes onward.

Since HR and BP did not change after CHIS, and BP fell while HR tended to rise after NTG, the product of systolic BP and HR was not significantly altered by either drug.

The time course of changes in LVFP is shown in figure 3. In all patients LVFP fell significantly after CHIS and NTG, but not P. Following NTG, onset of action was apparent at 5 minutes and peak reduction of 5.1 mm Hg (19.5%) occurred at 10 minutes. At 15 minutes LVFP was still significantly down, but by 20 minutes the 2 mm Hg reduction was no longer significant. The observed changes in LVFP after NTG closely paralleled the changes in BP after NTG. Following CHIS, LVFP was also significantly down by 5 minutes, with peak reduction of 8.6 mm Hg (32.7%) occurring at 15 minutes, and significant reduction persisting for three hours. When the groups were compared to each other, CHIS produced significantly lower LVFP compared to P from 5 through 180 minutes (P < 0.05), while NTG differed significantly from P (P < 0.05) only at 10 and 15

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**Figure 1**

Heart rate changes after chewable isosorbide dinitrate (IS) and sublingual nitroglycerin (NTG) in patients with heart failure. N = 7 for nitroglycerin, 8 for other groups. Values = mean ± se. P = placebo.

**Figure 2**

Changes in systolic (top) and diastolic (bottom) blood pressures after chewable isosorbide dinitrate (IS) and sublingual nitroglycerin (NTG) in patients with heart failure. N = 7 for nitroglycerin, 8 for other groups. Mean values are plotted. P = placebo. Solid circles indicate no significant difference from time 0, open squares indicate P < 0.02, open triangle indicates P < 0.05.
minutes. During the period of peak CHIS effect on LVFP, that is 15 through 30 minutes, differences between CHIS and NTG were also significant (P < 0.01). Thus, CHIS lowered LVFP as rapidly as NTG, but its peak effect was greater and its duration was nine times longer.

Cardiac output increased after both NTG and CHIS in the two patients in whom it was measured. In one patient it rose from 2.15 L/min to 2.92 L/min after NTG, and from 1.73 L/min to 3.29 L/min after CHIS. In the other patient, control cardiac output of 3.86 L/min increased by 0.62 L/min after NTG and 0.90 L/min after CHIS. Since only two patients were involved, statistical analysis was not performed on these data.

Discussion

The present study demonstrates that CHIS is an effective long-acting vasodilator which decreases LVFP in patients with heart failure for three hours without altering HR or BP and without producing untoward effects in this group of patients. Although cardiac output was measured in only two patients in this study, it did increase in both after NTG or CHIS.

Nitrates have a vasodilator effect on both arteries and veins. In normal individuals and in those with mild heart failure, reduction of arterial resistance would not be expected to result in much augmentation of stroke volume, whereas reduction of venous return would reduce stroke volume. Therefore, nitrates lower cardiac output in these subjects. In contrast, patients with severe heart failure respond to reduction of arterial resistance with a rise in stroke volume, whereas a fall in venous return should not greatly reduce stroke volume. Therefore, nitrates should increase cardiac output in these patients, as they did in two patients in the present series.

Vasodilatation also occurred after NTG, but the effects were short lived and HR increased while BP fell more than with CHIS. By virtue of its similar onset of action but much greater duration CHIS appears preferable to NTG. It has been suggested that CHIS has other theoretical advantages over NTG. Chewing of the tablet results in salivary stimulation and exposure to greater absorptive surface area; it is also more palatable and psychologically acceptable to the patient.

Reasons for the observed hemodynamic differences between NTG and CHIS are not apparent from this study. Venodilation might be greater after NTG, but we observed a greater fall in LVFP after CHIS. Venous capacitance measurements, which we did not do, would be needed, however, to demonstrate different venous effects between the two drugs. It is possible that NTG exerts potent effects more rapidly, resulting in greater reflex sympathetic stimulation which tends to restore BP and LVFP while increasing HR. Our earliest observations were made five minutes after drug administration, and although BP was significantly reduced by NTG at that point, the BP could have fallen to an even lower level earlier, and we were observing a rise back toward control at 5 minutes. Detry has demonstrated venous relaxation and tachycardia evident within 1–2 minutes after sublingual NTG with peak effects at 2–3 minutes.

Similar responses in the arterial circulation, measured by plethysmography, have been reported and the duration of such effects has been 15–20 minutes. The differences between NTG and CHIS resemble those between NTG and amyl nitrite; this latter agent has been shown to elicit more powerful sympathetic reflexes because of its earlier more potent effects on BP in comparison to NTG.

Although the present study was carried out in patients with heart failure, our observations are pertinent to angina pectoris, for which the nitrates are most commonly used. Acute attacks are generally treated with NTG while longer acting nitrates are used prophylactically. Since the anti-anginal effect of
the nitrates is at least in part due to a reduction in left ventricular pressure and volume\textsuperscript{21-23} then CHIS could be a suitable agent for both acute attacks and prevention of subsequent ones.

In comparison to the other forms of isosorbide dinitrate CHIS has the same advantages over the sublingual form that it has over NTG. When given sublingually isosorbide dinitrate has a delayed onset of action compared to NTG, but a duration of action of 1–2 hours on both exercise-induced angina and hemodynamic variables.\textsuperscript{24}–\textsuperscript{28} Oral isosorbide dinitrate has a longer duration of action than CHIS, but a more delayed onset; although we have demonstrated adequate absorption of the oral form in patients with heart failure, it is possible that abnormal hepatic function favorably influenced our results in those studies.\textsuperscript{11} Therefore, in certain situations where absorption of the oral form is questionable, CHIS may be used and administered more frequently. We still feel, however, that oral isosorbide dinitrate is the preferred agent for maintenance vasodilator therapy of heart failure because of its longer action requiring less frequent administration thereby encouraging better patient compliance with the treatment regimen. Of course, other currently existing vasodilators or new ones to be developed may supplant isosorbide dinitrate as their efficacy is demonstrated in the future.

The circulatory response to single doses of nitrates should have a beneficial effect in patients with heart failure. In patients with intractable heart failure, chronic vasodilator therapy appears to have a salutary effect on the clinical course.\textsuperscript{4, 10, 18} The rational application of nitrate therapy in patients with less severe heart failure depends on the demonstration that nitrate action persists during chronic administration and that clinical response can be demonstrated in a randomized controlled study. In general, the nitrates should be considered as adjuncts to conventional therapy of heart failure, and not replacements for digitalis or diuretics. Rather than increasing dosage of these latter agents, which are often associated with unwanted side effects and toxicity, addition of nitrates may be helpful and safer in some patients, especially those with intractable heart failure.

The role of the nitrates in acute myocardial infarction remains controversial in view of recent conflicting evidence.\textsuperscript{5, 9} Because of the risk of a precipitous fall in systemic blood pressure or a possible reduction of an already low cardiac output, the nitrates should be used with extreme caution and with appropriate hemodynamic monitoring in acute myocardial infarction. At present, intravenous infusions of potent short-acting vasodilators such as nitroprusside, are preferred because their effects can be more easily controlled and undesirable side effects usually disappear within minutes of stopping the infusion.\textsuperscript{5, 8}

In summary, CHIS is an effective, long-acting vasodilator intermediate between the sublingual and oral nitrates in its duration of action. It possesses certain advantages over NTG and may be substituted for it as acute vasodilator therapy of heart failure under conditions in which use of the potent intravenous agents may not be advisable. Along with oral isosorbide, CHIS provides an alternative for use in chronic impedance-reducing therapy; both these agents, because of their favorable hemodynamic effects, also merit further objective evaluation, particularly at larger doses, as anti-anginal drugs.

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