Hemodynamic Effects of Orally Administered Isosorbide Dinitrate in Patients with Congestive Heart Failure

By Joseph A. Franciosa, M.D., Esteban Mikulic, M.D., Jay N. Cohn, M.D., Ernesto Jose, M.D., and Anastacia Fabie, M.D.

SUMMARY
The efficacy of orally administered isosorbide dinitrate (IS) has been questioned. Recently vasodilators have been shown to lower left ventricular filling pressure (LVFP) and raise cardiac output in heart failure. In the present study oral IS was evaluated in 12 patients with high LVFP due to heart failure. After right heart catheterization, patients with LVFP > 14 mm Hg were randomized double-blind to receive either 20 mg IS or placebo (P). Supine heart rate (HR), arterial pressure (BP), and LVFP were monitored for five hours. After this the alternate drug (P or IS) was given, followed by five more hours of monitoring. In the 12 patients after receiving IS, LVFP reached a peak reduction of 6.7 mm Hg (~26%, P < 0.005) at 30 min. Significant reduction persisted for 4.5 hours. Blood pressure fell concomitantly with the LVFP. At 60 min HR was unchanged, systolic BP was reduced by 8.9 mm Hg (P < 0.025) and diastolic BP by 6.3 mm Hg (P < 0.005). In the ten patients receiving P, control values were not significantly different from those given IS, and after receiving P, HR, BP, and LVFP failed to change significantly over the next five hours. Thus, oral IS produces a sustained reduction in LVFP and therefore merits further evaluation as chronic therapy for left ventricular failure.

Additional Indexing Words:
Long-acting nitrates  Vasodilators  Impedance reduction

Efficacy of the long-acting nitrates remains a controversial issue. Isosorbide dinitrate (IS), which is used commonly in the treatment of angina pectoris, has not been found consistently effective in this disorder.1-7 Subjectivity of the anginal syndrome to various kinds of interventions makes it extremely difficult to interpret symptomatic responses to drugs.8 This factor plus the lack of uniformity and the inadequacies of protocol design have made the objective evaluation of long-acting anti-anginal agents difficult and inconclusive.9 Even though efficacy of IS given sublingually has been objectively demonstrated by hemodynamic measurements,10,11 considerable doubt remains regarding its activity following oral administration because of possible rapid hepatic biotransformation.12

It has recently been shown that vasodilators reduce left ventricular filling pressure (LVFP) and improve hemodynamics in patients with refractory heart failure or acute left ventricular dysfunction complicating acute myocardial infarction.13-18 Since LVFP falls significantly during administration of the vasodilators sodium nitroprusside13,14,15 and nitroglycerin,19 monitoring changes in LVFP should be an objective way to assess the effects of other vasodilating agents. Also, because the availability of an effective long-acting vasodilator appears desirable, the present study was initiated in an attempt to find such a drug and to evaluate LVFP monitoring as a method for demonstrating its efficacy. Our preliminary experience in patients with heart failure suggested that oral IS might be such an agent.

Methods
Patients with clinical evidence of congestive heart failure (dyspnea, S3 gallop, jugular venous distention, edema, and pulmonary venous engorgement on physical or radiological examination) secondary to primary myocardial disease, coronary artery disease, or acute myocardial infarction were selected for study. The diagnosis of primary myocardial disease was made in patients with a history of marked alcohol abuse and a lack of clinical evidence to support any other etiology for their heart disease. All but one of these patients underwent cardiac catheterization and coronary arteriography, which failed to establish any other etiology. The diagnosis of coronary artery disease was made in patients with documented previous myocardial infarction and/or significant occlusive lesions on coronary arteriography.
Acute myocardial infarction was documented by typical history with serial electrocardiographic and serum enzyme changes. Patients with other forms of heart disease or significant pulmonary disease were excluded.

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 patients who were taking maintenance doses of digitalis were given their daily dose prior to study. All diuretics, vasodilators, and antihypertensive medications were withheld.

After obtaining written informed consent, right heart catheterization was performed by inserting a Swan-Ganz flow-directed balloon-tipped catheter percutaneously via an antecubital or femoral vein. The catheter was connected to a P23Db Statham pressure transducer which was zeroed at the level of the mid-axillary line with the patient supine; all pressures were recorded in this position on a Hewlett Packard multichannel direct writing recorder. Heart rate (HR) was measured from the electrocardiogram and systemic arterial blood pressure (BP) was measured by the standard cuff technique. An automatic ultrasonic blood pressure recording apparatus (Arteriosonde) was used in cases where it gave readings in agreement with the first few manual measurements.

Occluded pulmonary arterial pressure or pulmonary arterial diastolic pressure was taken as LVFP. If control LVFP averaged 14 mm Hg or higher on three successive readings taken at 5 min intervals, the patient was then given either IS, 20 mg orally, or an identical appearing placebo (P). Left ventricular filling pressure, HR, and BP were recorded every 5 min for the first half hour and every 15 min for the next 4.5 hours after drug administration. After the first 5-hour period, if LVFP was 14 mm Hg or greater, the second drug was given and measurements repeated in the same manner for 5 more hours. The drug dosage and duration of observations were based on our preliminary clinical experience.

The order of drug administration was randomized in double blind fashion by a coin toss following control measurements. The randomization procedure was performed by a person not involved with the study and the results were not made known until the study was completed and all data calculated.

All statistical analysis was performed by using Student's t-test.

**Results**

Clinical characteristics of the patients studied are presented in table 1. All subjects were males averaging 53.8 years of age. With the exception of four who had acute myocardial infarctions, all were receiving maintenance doses of digitalis up to the time of study. No one had the clinical picture of acute pulmonary edema or cardiogenic shock. No patient developed arrhythmia, chest pain, headache, dizziness or other complications during the study period. One patient, number 9, with acute myocardial infarction eventually died; he went into cardiogenic shock 12 days after being studied, recovered from this, but later died from pneumonia.

Control values for LVFP, HR, and BP before each drug administration are also shown in table 1. There were no statistically significant differences between pre-IS and pre-P control values for any parameter measured. In addition, when patients receiving IS as their first drug were compared to those given P first, there were still no significant differences. In patients receiving IS first, control values prior to P administration were not significantly different from pre-IS controls. Two patients were given only one drug, which turned out to be IS in both instances. One of these was unwilling to continue for the second 5-hour period because of fatigue and restlessness. In the other case,

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Characteristics and Control Hemodynamics</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Control LVFP</th>
<th>Control BP</th>
<th>Control HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. HW</td>
<td>59</td>
<td>AMI</td>
<td>15</td>
<td>6</td>
<td>102</td>
</tr>
<tr>
<td>2. AS</td>
<td>49</td>
<td>CAD</td>
<td>40</td>
<td>120</td>
<td>102</td>
</tr>
<tr>
<td>3. RM*</td>
<td>58</td>
<td>PMD</td>
<td>38</td>
<td>136</td>
<td>110</td>
</tr>
<tr>
<td>4. GL</td>
<td>32</td>
<td>AMI</td>
<td>14</td>
<td>140</td>
<td>110</td>
</tr>
<tr>
<td>5. CW</td>
<td>50</td>
<td>CAD</td>
<td>23</td>
<td>118</td>
<td>98</td>
</tr>
<tr>
<td>6. TL*</td>
<td>78</td>
<td>AMI</td>
<td>23</td>
<td>125</td>
<td>81</td>
</tr>
<tr>
<td>7. LS*</td>
<td>53</td>
<td>PMD</td>
<td>32</td>
<td>130</td>
<td>96</td>
</tr>
<tr>
<td>8. CD*</td>
<td>46</td>
<td>PMD</td>
<td>23</td>
<td>107</td>
<td>89</td>
</tr>
<tr>
<td>9. CL</td>
<td>59</td>
<td>AMI</td>
<td>25</td>
<td>103</td>
<td>110</td>
</tr>
<tr>
<td>10. JH*</td>
<td>57</td>
<td>CAD</td>
<td>47</td>
<td>90</td>
<td>88</td>
</tr>
<tr>
<td>11. CL*</td>
<td>52</td>
<td>PMD</td>
<td>14</td>
<td>147</td>
<td>93</td>
</tr>
<tr>
<td>12. JH</td>
<td>52</td>
<td>PMD</td>
<td>18</td>
<td>94</td>
<td>114</td>
</tr>
</tbody>
</table>

**Mean** 25.9 22.1 117.2/85.5 112.9/84.6 99.7 93.0

**Standard deviation** 11.0 6.6 19.1/13.5 17.2/12.8 17.6 15.2

* = patient received isosorbide dinitrate before placebo.

**Abbreviations:** LVFP = left ventricular filling pressure (mm Hg); AMI = acute myocardial infarction; BP = systemic arterial blood pressure (mm Hg); CAD = coronary artery disease; HR = heart rate (beats/min); PMD = primary myocardial disease; IS = isosorbide dinitrite; P = placebo.
LVFP remained below 14 mm Hg at the end of the first 5 hours.

The time course of changes in LVFP following IS and P is shown in figure 1 which depicts the mean values for the group at each point in time. Within 5-10 min after IS administration LVFP was down in several patients, and by 20 min it had fallen an average of 3 mm Hg (\( P < 0.01 \)). Peak reduction of 6.7 mm Hg (-26%) (\( P < 0.005 \)) was observed at 30 min. The peak effect persisted for 2 hours (\( P < 0.001 \)) following drug administration when LVFP began to rise toward control levels. The last point of significant reduction of LVFP by 4.1 mm Hg (\( P < 0.025 \)) was observed at 4.5 hours.

No significant change in LVFP occurred during the five hours following P, although considerable fluctuation was seen. In individual patients LVFP varied as much as 10 mm Hg above or 9 mm Hg below the control values which demonstrated a wide range of spontaneous variability.

When the two groups were compared to each other instead of their respective controls, LVFP was 3.2 mm Hg lower for IS at 25 min (\( P < 0.025 \)). A peak difference of 7.7 mm Hg between IS and P occurred at 30 min (\( P < 0.005 \)), and the differences between the two groups remained significant for 4.5 hours.

The reduction of LVFP following IS in patients with acute myocardial infarction was less pronounced but still significant. At 1.5 hours after IS, LVFP was down 2.8 mm Hg (\( P < 0.025 \)) in patients with acute myocardial infarction and 8.5 mm Hg (\( P < 0.001 \)) in those without infarction. Peak reduction was 4 mm Hg at 3 hours in infarct patients. The difference in LVFP reduction between patients with and without acute myocardial infarction was not significant. It should be noted that LVFP averaged 29.4 mm Hg before IS in non-infarct patients and only 19.3 mm Hg before IS in patients with acute myocardial infarction. Thus, it might be expected that the absolute fall of LVFP in the infarct patients would be less.

Mean values for systolic and diastolic BP changes following drug administration are shown in figure 2. Both systolic and diastolic BP were significantly reduced after IS, but no significant change was seen after P. Although both pressures exhibited peak reductions at about 1 hour following IS, significant changes in systolic BP lasted only 2 hours, while diastolic BP was still down 3.3 mm Hg (\( P < 0.025 \)) at 4 hours. Systolic BP was reduced 8.9 mm Hg (-8%), \( P < 0.025 \) 1 hour after IS, and diastolic BP was down 6.3 mm Hg (-7%, \( P < 0.005 \)) at peak effect. Both
systolic and diastolic BP were significantly lower for IS when compared to P at peak effect (P < 0.025), and the BP response in patients with acute myocardial infarction was no different than for the non-infarct group.

Changes in HR are plotted in figure 3. Although none of the changes were statistically significant in either group, HR tended to decrease following IS and increase after P. However, at 1 hour after receiving the drug, HR was down 4 beats/min for IS and increased by 5.3 beats/min for P. This difference between groups was significant (P < 0.025). The product of HR times systolic BP was reduced by 16% (P < 0.025) 1 hour after IS and was increased by an insignificant degree (7%) 1 hour after P.

Discussion

Early enthusiasm for IS as an effective long-acting vasodilator was based on studies showing symptomatic relief of angina pectoris.1, 20, 3 These early reports were criticized because of a lack of adequate controls and use of subjective evaluative methods.4 With the addition of exercise testing as a measure of response, the results remained inconclusive.3, 5, 6, 9 By adopting more standardized reproducible exercise testing methods, Goldstein et al. were able to demonstrate increased exercise tolerance following sublingual IS.7 They found that IS was comparable to equivalent doses of nitroglycerin in both degree and duration of improved tolerance to exercise. Their findings were confirmed by others.4 Sweatman et al. compared the hemodynamic effects as well as exercise response after sublingual IS and nitroglycerin.10 One hour after IS exercise tolerance was increased and pulmonary capillary wedge pressure was significantly reduced. Nitroglycerin was ineffective one hour after its administration. Similar results have been recently reported by Willis et al. who observed a reduced pulmonary artery diastolic pressure one hour after sublingual IS, while systemic pressure remained down for 2-4 hours.11

It appears, therefore, based on objective data, particularly hemodynamic responses, that sublingual IS is an effective vasodilator. Orally administered IS, on the other hand, has not yet been demonstrated as clearly effective. Russek reported improved exercise tolerance lasting 2 hours after oral IS. Considerable doubt regarding the effectiveness of orally administered nitrates was raised by Needleman’s experiments,12 which showed that IS given by mouth or into the portal vein of rats yields only minute plasma concentrations of unaltered IS and no hypotensive activity. The results were attributed to biotransformation of the drug by hepatic enzymes, which the authors found present in abundant amounts in human liver as well. Other authors found similar results after giving IS by mouth to dogs, but they also demonstrated high levels of IS metabolites which disappeared much more slowly than unaltered IS.21 Pharmacological activity of these metabolites was postulated but not conclusively demonstrated. Other studies in awake dogs have shown that oral IS produces a significant reduction of pulse pressure.20

Since changes in LVFP provide a more objective measure of pharmacological activity than relief of angina, the assay system used in the present study should allow a more precise demonstration of the efficacy of oral IS in man. The present study shows that LVFP falls significantly within 20 minutes after oral administration of IS in patients with elevated LVFP due to heart failure. This effect persists for up to 4½ hours and is not seen following P in the same patients. Systolic and diastolic BP also fall significantly after IS, but not after P. These changes constitute conclusive evidence that orally administered IS is absorbed and is pharmacologically active, either in its altered or unaltered state.

No important side effects were seen after 20 mg IS by mouth. Although some patients in this series had low blood pressure to start with, none developed symptomatic hypotension. This was probably due, at least in part, to the fact that blood pressure was underestimated in some of the more severely ill patients.22 Reduction of blood pressure in patients with acute myocardial infarction might also be questioned because of possible coronary underperfu-
evaluation of pharmacological clinical failure; therefore, Dr. Alberto Rosenberg of ICI America Inc. and Dr. Clarence Denton of Ives Laboratories.

Acknowledgment

The authors wish to express their gratitude to Miss Eleanor Garlisi, R.N., Mrs. Helen Bazaz, R.N., and Miss Sally Rubenstone, R.N., for their skillful and valuable technical assistance.

Supplies of Isosorbide Dinitrate were kindly made available by Dr. Alberto Rosenberg of ICI America Inc. and Dr. Clarence Denton of Ives Laboratories.

References

1. SHEBER DA, GELB II: The clinical pharmacology of isosorbide dinitrate: A unique new nitrated polyalcohol. Angiology 12: 244, 1961
2. BUNN WH, CHREMONOS AN: Clinical evaluation of sublingual nitrates. Angiology 14: 48, 1963
20. HASTINGS SG: Bioavailability studies of nitrates in the dog. Arch Int Pharmacodyn Ther 203: 117, 1973
Hemodynamic Effects of Orally Administered Isosorbide Dinitrate in Patients with Congestive Heart Failure

JOSEPH A. FRANCIOSA, ESTEBAN MIKULIC, JAY N. COHN, ERNESTO JOSE and ANASTACIA FABIE

Circulation. 1974;50:1020-1024
doi: 10.1161/01.CIR.50.5.1020

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/50/5/1020

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/