Pharmacokinetic–Hemodynamic Studies of Intravenous Nitroglycerin in Congestive Cardiac Failure

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SUMMARY The expanding role of intravenous nitroglycerin (GTN) in the management of critically ill hospitalized patients demands a clear knowledge of its pharmacodynamics and kinetics in both normal and diseased states. Accordingly, we studied 16 patients with congestive cardiac failure to establish the relationship between blood levels of GTN and its physiologic effects during and after an i.v. infusion. The end point of this study was either a greater than 25% fall in pulmonary capillary wedge pressure or more than a tenfold increase over the initial GTN infusion rate. Infusion rate of GTN and blood concentration correlated well ($r = 0.75, p < 0.001$). Patients were divided into two groups based on their blood GTN concentration. Group 1 patients ($n = 8$) achieved blood GTN concentrations of 1.2–11.1 ng/ml and all reached the hemodynamic end point. The minimum effective blood GTN concentration was 1.2 ng/ml at an infusion rate of 15 μg/min. Group 2 patients ($n = 8$) had blood levels greater than 11.1 ng/ml and only three achieved the hemodynamic end point. Group 2 had greater systemic venous congestion than group 1 (right atrial pressure 19 ± 4 mm Hg (SD) vs 10 ± 4 mm Hg [$p < 0.001$]). In addition, group 2 had lower total body clearance of GTN (3.6 ± 1.8 l/min) than group 1 (13.8 ± 5.8 l/min) ($p < 0.005$). The low clearance of GTN in group 2 patients may be explained in part by impaired hepatic metabolism secondary to severe systemic venous congestion. Complete blood GTN data were available on five patients after cessation of the GTN infusion and revealed a short half-life of 1.9 minutes. Some patients failed to reach the hemodynamic end point with high infusion rates of GTN (220–440 μg/min), and blood levels of 42.2–481.3 ng/ml. There was no evidence of toxicity despite these high GTN blood levels.

THE TRADITIONAL ROLE of nitroglycerin (GTN) as therapy for angina pectoris has become more diversified in the last decade. The use of this agent in hospitalized patients has become widespread and includes patients with acute myocardial infarction, congestive cardiac failure, unstable angina pectoris, and patients undergoing cardiac surgery. This enthusiasm for its use has been generated by an appreciation of its protective effects on ischemic myocardium and by recent understanding of the importance of the role of the peripheral circulation in congestive cardiac failure. The increasing role of GTN in such a wide variety of clinical problems, particularly those that relate to the critically ill, demands a clear knowledge of its pharmacodynamics and kinetics in both normal and diseased states.

In our previous studies, we have observed as much as a tenfold variation in dose required to produce similar physiologic effects among individual patients. This finding suggested that there might either be enhanced GTN metabolism or target organ resistance in patients who require the highest doses. The recent development of a method for measuring blood GTN permitted us to address these problems. The objectives of the current study in patients with congestive cardiac failure were (1) to establish the relationship between blood levels of GTN and its physiologic effects and (2) to investigate the pharmacokinetics of GTN administered by i.v. infusion.

Materials and Methods

Patient Population

Sixteen patients with congestive cardiac failure formed the study group. Table 1 gives pertinent characteristics of the patients. All patients had congestive cardiac failure and, with the exception of three who were studied within 48 hours of an acute myocardial infarction, were in functional class III or IV and refractory to conventional therapy, including digoxin and furosemide. Six patients had received isosorbide dinitrate therapy for at least 3 weeks before the study. All had radiographic documentation of heart failure as defined by cardiomegaly and pulmonary venous congestion and confirmed by control hemodynamics as outlined in table 2 and figures 1 and 2. All drugs except digoxin and insulin were withheld for at least 24 hours before the study.

After informed consent was obtained, patients were instrumented for hemodynamic monitoring in a standardized fashion. This included placing a Swan-Ganz...
Table 1. Patient Population Characteristics

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Duration of CHF</th>
<th>Previous nitrate use</th>
<th>Renal function</th>
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<td>56</td>
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<td>&lt; 1 mo after MI</td>
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<td>Normal</td>
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<td>RA</td>
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Abbreviations: ASHD = arteriosclerotic heart disease; MI = myocardial infarction; ISDN = isosorbide dinitrate; BUN = blood urea nitrogen (mg%); Cr = creatinine (mg%); ↑ = elevation.

Thrombolysis catheter in the pulmonary artery and a teflon cannula in the radial artery. Right atrial (RAP), pulmonary arterial (PAP) and pulmonary capillary wedge pressures (PCWP) obtained by balloon occlusion, as well as systemic arterial pressure, were monitored. Cardiac output (CO) was measured at least in duplicate by the thermodilution technique with injection of 10 ml of ice-cold 5% dextrose in water into the right atrium. After a control period of 20–30

Figure 1. Composite plot of hemodynamic response to intravenous nitroglycerin at peak infusion rate (n = 16). HR = heart rate; bpm = beats/min; MAP = mean arterial pressure; PCW = pulmonary capillary wedge pressure; CI = cardiac index. All values represent mean ± SD. Asterisks represent statistically significant differences from control.

Figure 2. Composite plot of hemodynamic response to intravenous nitroglycerin at peak infusion rate (n = 16). SI = stroke index; TTI = tension-time index; TPR = total peripheral resistance; TMG = transmyocardial gradient.
minutes during which hemodynamic measurements were shown to be reproducible, i.e. GTN was infused at an initial rate of 15-20 μg/min. The aim was to reduce PCWP by at least 25% of its control value and the infusion rate was increased in a stepwise fashion (50% increments of prior rate) every 10-15 minutes until the desired hemodynamic end point was achieved or a greater-than-tenfold increment in the initial infusion rate had been reached. Hemodynamic monitoring was performed during the infusion and complete measurements including CO were obtained at the peak rate. The infusion was maintained at the peak rate for at least 15 minutes because our previous experience has shown that a hemodynamic steady state was achieved by this time.* The infusion was then discontinued and monitoring performed for an additional 15-30 minutes until values returned to control levels.

Derived calculations were performed using the formulas SI = CI/HR, TTI = HR × SBP as modified by Monroe,⁰ TPR = (MAP – RAP)/CO, TMG = ARTd – PCWP, where SI = stroke index (ml/beat/m²), CI = cardiac index (l/min/m²), TTI = tension-time index (mm Hg/min × 10⁻¹), SBP = systolic blood pressure (mm Hg), TPR = total peripheral resistance (units), MAP = mean arterial pressure (mm Hg), CO = cardiac output (l/min), RAP = right atrial pressure (mm Hg), TMG = transmyocardial gradient (mm Hg), ARTd = arterial diastolic pressure (mm Hg) and PCWP = pulmonary capillary wedge pressure (mm Hg).

Arterial blood samples for GTN were withdrawn from the radial cannula during the control period and at the time of the peak infusion; in 11 of the study group, additional samples were taken 2, 5 and 10 minutes after cessation of the infusion.

The blood samples were immediately centrifuged at 5°C and the decanted plasma was frozen at −20°C. Subsequent analysis was performed using a gas-liquid chromatograph with isosorbide dinitrate as the internal standard.*

Pharmacokinetic parameters were calculated using the formulas:¹¹

\[ C_{ss} = \frac{\text{infusion rate}}{\text{clearance}} \]

\[ V_d = \frac{\text{clearance} \times t_{1/2}}{0.693} \]

where \( C_{ss} \) is steady-state concentration and \( V_d \) is volume of distribution.
GTN was prepared for intravenous use as a 0.5% solution in ethanol. A 9.5% lactose mixture (Parke-Davis) (6.3 g) was added to ethyl alcohol (99%) to a total volume of 120 ml. The alcoholic supernatant was decanted and passed through a 0.22-μ millipore filter. The solution was assayed using a spectrophotometric technique before being reassayed using our gas-liquid chromatograph method.9 Immediately before use, the GTN solution was added to 5% dextrose in water (in glass bottles) to produce a concentration of 100 μg/ml.

Hemodynamic changes from control produced by i.v. GTN at the peak infusion rate were analyzed using the paired \( t \) test. Analysis of differences between groups 1 and 2 (table 2) was performed using an unpaired \( t \) test. The relationship between measurements in figure 3 and the blood GTN concentrations and infusion rates (table 2) was estimated using a linear regression analysis, and significance was tested using Fisher’s \( F \) test.

**Results**

Figure 1 is a composite plot of hemodynamic data during the control period and at the peak infusion rate of GTN. There was no significant change in HR. MAP fell from 90 to 83 mm Hg (\( p < 0.001 \)). PCWP fell 22.7, from 28 to 20 mm Hg (\( p < 0.005 \)). RAP fell from 14 ± 6 to 9 ± 4 mm Hg (\( p < 0.001 \)).

![Figure 3. A semilog plot of blood nitroglycerin (GTN) concentration as a percentage of peak value against minutes after cessation of infusion in five patients (\( r = 0.95 \), \( p < 0.001 \)).](http://circ.ahajournals.org/)

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**Table 2.** (Continued)

<table>
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<th>CI (l/min/m²)</th>
<th>CI (%)</th>
<th>TPR (units)</th>
<th>TPR (%)</th>
<th>Blood GTN (ng/ml)</th>
<th>Total body clearance (l/min)</th>
<th>( \frac{1}{2} ) (min)</th>
<th>Vd (l)</th>
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</table>

NS NS NS NS < 0.005
There was a small but significant increase in SI, from 23 to 27 ml/beat/m² (p < 0.02), a slight but significant fall in TTI, from 1094 to 1009 mm Hg × 10⁻¹ (p < 0.05), a fall in TPR from 24 to 19 units (p < 0.05) and no change in TMG (fig. 2).

Individual hemodynamic and pharmacokinetic data are given in table 2. The patients were divided into two groups based on their blood GTN concentrations (assumed to be at steady state) at the peak GTN infusion rate. Group 1 included patients whose blood levels were ≤11.1 ng/ml; in all of these the target of a 25% fall in PCWP from control was reached. The average fall was 36% and there was a roughly parallel fall in RAP that averaged 35% in this group. There was an excellent correlation between blood GTN concentration and infusion rate for patients in this group (r = 0.95, p < 0.001).

In group 2 (blood GTN levels >11.1 ng/ml) there was a wide range of infusion rates and corresponding blood levels; the average decline in PCWP for this group was 21%. Of the three patients who achieved the hemodynamic end point, BK had already achieved a 27% decline in PCWP at a GTN infusion rate of 59 μg/min. NY showed only 10% and 13% declines in PCWP at infusion rates of 110 μg/min and 310 μg/min, respectively, and BR showed a 21% decline at 110 μg/min. We analyzed the five patients who failed to achieve a 25% fall in PCWP. JO and HA did not receive a tenfold increase over the initial infusion rate due to a technical error but still achieved blood GTN concentrations of 19.9 ng/ml and 18.7 ng/ml, respectively. CA had a 17% fall in PCWP at an infusion rate of 220 μg/min and no further change at 440 μg/min, and MO showed a 23% fall in PCWP at an infusion rate of 110 μg/min, with no further alteration at 440 μg/min. RAP fell in patients JO and CA to a much greater degree (30% and 45%) than did the PCWP (11% and 16%, respectively). The correlation between blood GTN concentration and infusion rate for group 2 was r = 0.66, p = NS. For all 16 patients analyzed together, the relationship was r = 0.75, p < 0.001.

Goldberg and co-workers suggested that patients with the highest systemic vascular resistance have the most favorable response to vasodilators. Therefore, we performed a linear regression analysis to assess the correlation between control TPR and the GTN-induced changes in PCWP, RAP and CI and TPR. The resultant r values were 0.07, 0.23, 0.37 and 0.56, respectively, in the 16 patients. A breakdown of this analysis — control TPR vs changes in PCWP, RAP, CI and TPR — revealed correlation coefficients of 0.02, 0.36, 0.39 and 0.68, respectively, in group 1 and 0.19, 0.15, 0.26 and 0.47, respectively, in group 2.

When the control hemodynamics of the two groups were compared (table 2) the PCWP was similar and the RAP in group 2 was significantly greater than in group 1 (19 ± 4 mm Hg vs 10 ± 4 mm Hg [p < 0.001]). Although the CI tended to be lower and the TPR higher in group 2, these values were not significantly different from those in group 1.

Three patients in group 1 had had previous nitrate therapy (RA, LI and KE). Of the three patients in group 2 who had had previous nitrate therapy, AJ and MO did not achieve the hemodynamic end point, while BR had a 29% fall in PCWP, but not until an infusion rate of 310 μg/min and a GTN concentration of 139 ng/ml were reached.

Total body clearance of GTN was calculated from the blood GTN concentration (assumed to be at steady state) and the corresponding infusion rate. In five patients adequate blood level data were obtained after cessation of i.v. infusion to permit half-life determinations. The disappearance of GTN from blood during a 10-minute period after cessation of infusion in these patients is shown in figure 3 as a semilog plot of blood GTN as a percent of peak value against minutes after cessation of infusion. The half-life calculated from the best fit line to this data is 1.9 minutes. In six additional subjects, “off data” were available and rapid disappearance of GTN from blood was confirmed; however, blood GTN was undetectable (< 0.5 ng/ml) before enough data could be obtained for kinetic analysis. In all instances GTN was either undetectable or less than 5% of its peak value 10 minutes after this infusion was terminated.

Assuming the blood GTN concentration to be at steady state, total body clearance of GTN was calculated using the appropriate infusion rate (table 2). Using the individually determined half-life determinations and clearance calculations, volume of distribution for GTN was calculated in the five patients in whom such data were available (table 2).

In contrast to the rapid disappearance of GTN from blood, return to control hemodynamic values was delayed and usually complete in 15 minutes. Hemodynamic and blood GTN data from patient CA during and after cessation of GTN infusion is displayed in figure 4. No further hemodynamic change was seen after that achieved at 220 μg/min, when a blood GTN level of 42.5 ng/ml was found. At 10 minutes after cessation of GTN, the blood level had fallen to 5.9 ng/ml, with only partial return of hemodynamics toward control values.

During these studies there were no untoward effects, such as severe sustained headache, undue flushing, nausea and vomiting or hypotension.

**Discussion**

This study demonstrates that i.v. GTN provides substantial hemodynamic benefit to patients with congestive cardiac failure. This is evident by the reductions in PCWP, averaging 29%, and the rise in both CI and SVR. There were associated reductions in MAP, TPR and TTI, without compromise in the coronary perfusion pressure as indicated by preservation of the TMG. Thus, cardiac performance improved with a reduction in oxygen cost and no impairment in coronary flow.

The summary hemodynamic data, however, conceal major differences in the response of individual patients. While high doses of GTN were administered to some patients in an attempt to reach the defined hemodynamic end point, there were instances in which this goal was not achieved. In patients CA and JO there was striking disparity between the effects of
GTN on right- vs left-sided filling pressures; GTN had a dominant effect on right-sided filling pressure. Patient CA had severe congestive cardiac failure secondary to chronic arteriosclerotic heart disease with previous remote infarctions, and his control hemodynamics were the most disordered of the group. Patient JO had evidence of dominant right ventricular dysfunction secondary to an inferior myocardial infarction that had occurred 48 hours previously. These observations suggest that in some instances the venodilator effect of GTN may not be effectively transmitted to the left side of the heart. The mechanism for this is not clear, but could relate to differing compliance characteristics of the two ventricles if there were asymmetrical distribution of myocardial disease.18

Our previous experience with i.v. GTN infusions in over 100 patients with congestive cardiac failure and acute myocardial infarction has shown that hemodynamic alterations rarely occur at infusion rates less than 15  μg/min. The blood GTN concentration of 1.2 ng/ml at this infusion rate defines the minimum effective concentration in this patient population.9 One-half of our patients had favorable hemodynamic responses at infusion rates of 15-94 µg/min; these rates of infusion were associated with blood nitroglycerin concentrations of 1.2-11.1 ng/ml, which appear to represent the therapeutic range (table 2). The peak blood levels after 0.6 mg of sublingual GTN in normal volunteers have been found to average 2.4 ng/ml by us and 1.6 ng/ml by others.7-8 At blood levels above 11.1 ng/ml, which were not associated with toxic effects, there was an attenuated response to GTN in many instances. This attenuation in the presence of high circulating blood levels indicates a failure of response in veins and arterioles and is not attributable to enhanced metabolism.

Previous studies provide conflicting data regarding the value of systemic vascular resistance as a marker of responsiveness to vasodilators.13, 18 The peripheral resistance proved to be of little value in predicting hemodynamic response to i.v. GTN in our patients.

We chose the change in PCWP as the indicator of hemodynamic response because it has provided the most predictable measure of drug effect in our studies.3, 9 Moreover, if the major effect of GTN is peripheral and predominantly on the venous capacitance bed, alterations in PCWP or RAP or both would be expected to be the most sensitive hemodynamic indicator of its physiologic effects.5, 17 If our criteria for response were applied to the patients in Goldberg's study, all would have been responders.19

There were six diabetics in the present study, and five were in group 2 (blood levels > 11.1 ng/ml). Small-vessel disease secondary to diabetes could have modified the hemodynamic response in these patients. On the other hand, the finding of attenuated or no response to GTN in our patients could not be related to duration of heart failure or previous nitrate exposure.18 Patients in group 2 had a substantially higher RAP than did those in group 1. It is possible that near-maximal peripheral venous distension in these patients reduced the capacity for further venodilatation.

The mechanism of this attenuated response to GTN at present is unclear. Needleman and Johnson10 hypothesize that both tolerance and resistance to GTN develop when oxidation of sulphydryl groups occurs in vascular receptors. Variability in the level of circulating catecholamines and angiotensin in patients with cardiac failure would also be expected to alter the response of the peripheral circulation to pharmacologic therapy.20, 21 Further work is required to examine how these factors affect the action of GTN and nitrate resistance.

There was a good correlation between infusion rate and blood GTN concentration.11 These data are at variance with those reported by Wei and Reid,16 who found no relationship between infusion rate and peripheral venous GTN concentration in five patients who received GTN infusions at rates of 37.5-175 µg/min. The highest plasma GTN level achieved in their study was 2.7 ng/ml. The basis for the disparity between their data and ours remains unclear but could relate in part to differences in GTN preparation, diverse patient populations, medication history and blood sampling site (venous vs arterial). Brymer and co-workers22 found a higher concentration of GTN in

![Graph](image-url)
arterial vs peripheral venous blood after sublingual GTN and suggested that this might be explained by prompt binding to vascular receptors.

Analysis of the clearance and volume of distribution calculations for GTN reveals that group 1 patients had a significantly higher clearance (13.8 l/min) than group 2 (3.6 l/min). The high blood levels and low clearance of GTN in group 2 may be explained in part by poor peripheral perfusion and impaired hepatic metabolism secondary to severe systemic venous congestion. 23, 24

The half-life of 1.9 minutes determined in this study is shorter than the value of 4.4 minutes estimated in our previous analysis of normal volunteers, who received 0.6 mg of sublingual GTN. 7 The values for clearance of nitroglycerin and volume of distribution in normal volunteers were found to be 28 l/min and 179 l/min, respectively. The calculations in the sublingual study assumed that GTN was given as a bolus and required that absorption of GTN be complete within 2 minutes and that 100% of the drug be absorbed sublingually. It is more likely that sublingual GTN absorption was incomplete and occurred over a longer time period. For these reasons the values calculated for half-life clearance and volume of distribution were probably overestimated.

This rapid disappearance of GTN from the blood has been shown in animal experiments using both a gas-liquid chromatograph assay technique and radioactive GTN. 25, 26 We recently studied the disappearance of GTN incubated at 37°C in fresh whole human blood and found a half-life of 6.4 ± 1.9 (SD) minutes. 26 Moreover, glutathione s-transferase, which catalyzes the metabolism of GTN, has been isolated from rat kidney, intestinal mucosa and human erythrocytes. The short half-life of GTN may be attributable to metabolism in several tissues.

In summary, this study of patients with congestive cardiac failure has shown (1) that a good relationship exists in most patients between infusion rates of GTN and blood concentrations; (2) that substantial hemodynamic benefit from i.v. GTN is achieved in some patients generally at infusion rates of 15-100 µg/min, with resultant blood levels of 1.2-11.1 ng/ml; and (3) that some patients exhibit primary resistance or an attenuated response to GTN.

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