Nitroglycerin Pharmacokinetics after Intravenous Infusion in Normal Subjects

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Abstract □ The purpose of this investigation was to examine the pharmacokinetics of nitroglycerin in normal volunteers after intravenous drug administration. Eight subjects (including one subject on two occasions) received a dose of ~0.6 mg iv of nitroglycerin at a rate of 18 μg/min. Plasma concentrations of intact drug during and after the infusion were determined using a GLC method. Intra- and intersubject variability in nitroglycerin plasma kinetics was substantial. Generally, however, plasma nitroglycerin disposition was characterized by: (*a*) a large apparent plasma clearance (0.3–1 liter/min/kg), (*b*) a large volume of distribution (~3 liters/kg), and (*c*) a rapid plasma half-life (~3 min). From the apparent volume of distribution obtained, plasma drug can be estimated to account for only ~1.3% of total drug in the body. Minor fluctuations in tissue distribution, which can be produced by a myriad of external and internal stimuli, could cause dramatic fluctuation in plasma nitroglycerin concentrations and, hence, in the calculated pharmacokinetic parameters. For example, in two subjects studied, plasma nitroglycerin concentrations oscillated to such an extent that pharmacokinetic analysis could not be performed. In some subjects, steady-state concentrations were not observed in spite of the apparent short plasma half-life, and rebound in plasma concentrations during the postinfusion phase were evident. These phenomena were also observed in other kinetic studies involving organic nitrates.

Keyphrases □ Nitroglycerin—pharmacokinetics, intravenous infusion in normal subjects □ Pharmacokinetics—nitroglycerin, intravenous infusion in normal subjects □ Vasodilators—nitroglycerin, pharmacokinetics, intravenous infusion in normal subjects

Sublingual nitroglycerin has been used extensively for the relief of acute attacks of angina pectoris. Recently, intravenous nitroglycerin was shown to be effective in patients with congestive heart failure following myocardial infarction, for the treatment of coronary artery spasm in patients with variant forms of angina, for the reduction of arterial hypertension during coronary artery bypass, and for the induction of controlled hypotension during surgery.

BACKGROUND

Although the hemodynamic response to nitroglycerin infusion has been studied extensively, little is known about nitroglycerin pharmacokinetics. Wei and Reid (1) reported plasma nitroglycerin concentrations in patients receiving intravenous infusions, but their data were limited to measurements of single plasma concentrations obtained after a 1-hr infusion. Recently, Armstrong *et al.* (2) studied nitroglycerin pharmacokinetics from arterial blood samples in patients with congestive cardiac failure. Their pharmacokinetic calculations of clearance and the volume of distribution also were based on one steady-state nitroglycerin concentration obtained at the time of the maximum infusion rate. Data was not presented to confirm that steady state was indeed achieved.

Nitroglycerin is known to have a high affinity for plastic materials used in intravenous infusion bags and administration sets (3–5). A significant fraction of the dose can be lost to the delivery system during intravenous nitroglycerin infusion, thus leading to significant errors in the estimation of pharmacokinetic parameters. Since the available literature on nitroglycerin kinetics (1, 2) does not make explicit reference to this factor, pharmacokinetic parameters generated from these reports may be subject to additional degrees of uncertainty.

The present investigation examined the pharmacokinetics of intravenously administered nitroglycerin in normal subjects. Methodological problems were avoided by preequilibrating the infusion administration sets with nitroglycerin solution and determining the actual dose infused into each subject directly from the nitroglycerin concentration in the infusion solution immediately before and after drug administration. Plasma nitroglycerin concentrations were determined during and after infusion. Additionally, noninvasive hemodynamic parameters were monitored during the study.

EXPERIMENTAL

Eight healthy, nonsmoking, male adult volunteers underwent normal screening for vital signs, ECG, and laboratory parameters. Exclusion criteria included: (*a*) history of abnormalities of the cardiovascular, renal, or hepatic systems, blood, GI tract, or endocrine organs or any other significant disease state; (*b*) drug addiction including chronic marijuana use or alcoholism; and (*c*) chronic use of any medication.

Screening for Nitroglycerin Hypersensitivity—Prior to the study and at least 1 week before receiving the nitroglycerin infusion, each subject was prescreened for nitroglycerin hypersensitivity. This screening was done by sublingual administration of 0.15-mg doses of nitroglycerin[1] at 0, 7.5, 15.0, and 22.5 min for a total dose of 0.6 mg. Subjects who did not show any adverse reactions or nitrate hypersensitivity were included.

Preparation of Infusion Solutions—Nitroglycerin[2] was supplied in 10-ml ampuls containing 5 mg of nitroglycerin in a buffered solution of 10% ethanol. Five milliliters of this solution was added to 100 ml of normal saline (0.9%) in a glass intravenous container just prior to use.

Saturation of Infusion Tubing—Nitroglycerin adsorption to the infusion tubing was minimized by using a short length of tubing and preinfusion to saturate adsorption sites. The infusion solution was drawn first into a 50-ml glass syringe, which then was connected with the infusion tubing[3]. With an infusion pump[4], 10 ml was infused through the tubing at a rate of 0.382 ml/min, which then was increased to 0.764 ml/min until an additional 4 ml flowed through the tubing. The final 2 ml from this preinfusion procedure was collected for drug content assay (preinfusion sample). Following completion of the infusion into the subject, another 2-ml sample of the infusion solution was collected (postinfusion sample). The concentration of nitroglycerin in these two samples was compared with a sample taken directly from the glass intravenous bottle.

Drug Administration—Nitroglycerin solution was infused into a peripheral forearm vein through a polytef catheter[5] at a flow rate of 0.764 ml/min for 32 min. The nitroglycerin concentration in the infusion solutions was ~22 μg/ml, and the infusion rate was ~18 μg/min. The actual rate and the total amount of nitroglycerin administered to each subject were calculated from the assayed concentration of the infusion solutions.

Blood Samples—Disposable plastic syringes, previously determined not to cause drug loss (5), were used to draw blood samples through a peripheral vein cannula[5] in the arm not used for infusion. Following blood withdrawal, the cannula was flushed with heparin (100 U/ml) in 0.9% sodium chloride. Samples (5 ml) were drawn at 0 (just prior to infusion), 10, 20, 32, 34, 36, 38, 42, 47, 52, 62, and 77 min. Following transfer to silanized glass culture tubes and immediate centrifugation, the plasma was

[1] USP tablets, 0.15 mg (1/400 gr), lot 2GL77A Eli Lilly & Co., Indianapolis, Ind.
[2] Nitroglycerin solution, lot no. 19743 clinical trial material, American Critical Care, McGaw Park, Ill.
[3] K50 extension tubing, 50.8 cm, Pharmaseal, Toa Alta, Puerto Rico.
[4] Model 940, Harvard Apparatus, Millis, Mass.
[5] Angiocath, 20 ga × 1¼ in., The Deseret Co., Sandy, Utah.

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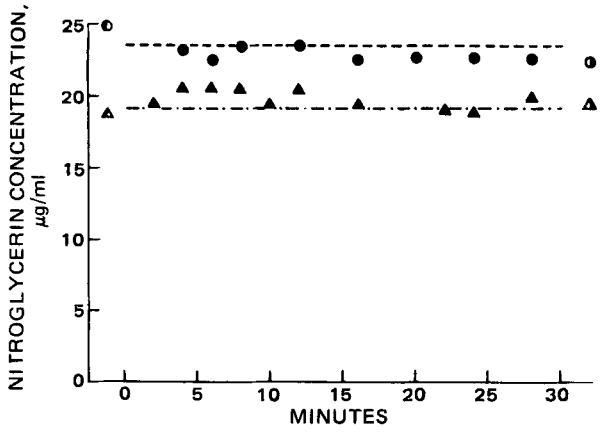

Figure 1—*Nitroglycerin concentration in infusion solutions during two simulated runs. Key to Run 1 samples: ◐, preinfusion; ●, during infusion; ◑, postinfusion; and ---, calculated infusion concentration. Key to Run 2 samples: ▲, preinfusion; ▲, during infusion; ▲, postinfusion; and –.–., calculated infusion concentration.*

separated and placed on ice until transported to the assay laboratory for storage at −20°. Sample analysis was performed as soon as possible and generally no later than 1 month after collection. These collection and storage conditions previously were shown to preserve nitroglycerin adequately (6).

Hemodynamic Monitoring—To ensure subject safety, hemodynamic status was determined periodically throughout the study. Blood pressure was determined by sphygmomanometry, and heart rate was measured manually or by an ECG monitoring device.

Assay—Plasma samples were assayed in duplicate according to a previously reported (7) GLC procedure. To increase sensitivity, the volumes of the plasma sample and the extraction solvent were increased to 0.5 ml. Caprylene was the internal standard. Recovery of nitroglycerin (~90%) was not affected by this modification.

A kinetic assay procedure (8, 9) was used to measure the nitroglycerin concentration of the infusion solutions.

Calculations—The actual infusion rate (k_0) for each subject was obtained by multiplication of the flow rate (0.764 ml/min) by the average of the nitroglycerin concentration in the preinfusion and postinfusion samples. In instances where no postinfusion sample was taken, the preinfusion concentration was used. The product of k_0 and the infusion time (32 min) yielded the total dose of nitroglycerin administered to each subject. Rebound in nitroglycerin plasma concentration occurred in several subjects, usually 10–20 min after infusion was terminated.

Estimates of pharmacokinetic parameters were obtained by using only those postinfusion data points that decreased in concentration chronologically. The elimination rate constant (K) was estimated by linear regression of the postinfusion log nitroglycerin plasma concentration *versus* time plot under such conditions. The area under the plasma nitroglycerin concentration *versus* time curve during the infusion period (AUC_{0-32}) was obtained using the spline method on a desk-top computer[6]. The postinfusion area ($AUC_{32-\infty}$) was computed by dividing the plasma nitroglycerin concentration at 32 min (C_{32}) by the estimated elimination rate constant. The total area then was obtained from the sum:

$$AUC_{0-\infty} = AUC_{0-32} + AUC_{32-\infty} \quad \text{(Eq. 1)}$$

The apparent systemic clearance (Cl_s) was calculated from:

$$Cl_s = \frac{\text{dose}}{AUC_{0-\infty}} \quad \text{(Eq. 2)}$$

and the apparent volume of distribution (V_d) was computed as:

$$V_d = \frac{Cl_s}{K} \quad \text{(Eq. 3)}$$

An additional estimate of the systemic clearance of nitroglycerin was obtained from:

$$Cl_s^* = \frac{k_0}{C_{32}} \quad \text{(Eq. 4)}$$

[6] Model 9825A, Hewlett-Packard, Fort Collins, Colo.

Table I—Nitroglycerin Concentration (Micrograms per Milliliter) in Infusion Solutions

Subject[a]	Bottle Concentration	Preinfusion Sample	Postinfusion Sample	Calculated Infusion Concentration
3	22.2	21.3	27.4	24.4
4	24.7	20.4	20.3	20.4
5A	24.5	21.0	22.5	21.8
5B	23.5	24.8	—[b]	24.8[c]
6	25.6	22.2	36.1	29.2
7	22.3	19.7	23.2	21.4
8	22.5	21.5	21.6	21.5
9	23.4	24.4	—[b]	24.4[c]
10	22.0	18.1	—[b]	18.1[c]
Mean	23.4	22.6	25.2	22.8
±*SD*	1.3	2.7	5.9	3.2

[a] Numbers arranged in chronological order of study. [b] Not determined; see text for explanation. [c] Concentration in preinfusion sample used.

RESULTS

An *in vitro* experiment was conducted to determine whether the adopted regimen for the saturation of the infusion tubing was adequate in delivering a constant nitroglycerin concentration during dosing. Figure 1 shows the results of two separate runs in which the infusion systems were presaturated as described and the concentration of nitroglycerin emerging from the infusion system during a simulated infusion was determined as a function of time. It is apparent that the procedure produced a relatively stable effluent nitroglycerin concentration during the 32 min of infusion. The infusion concentration calculated from the mean of the preinfusion and postinfusion samples appeared to represent the actual infusion concentration adequately. The mean of the absolute difference

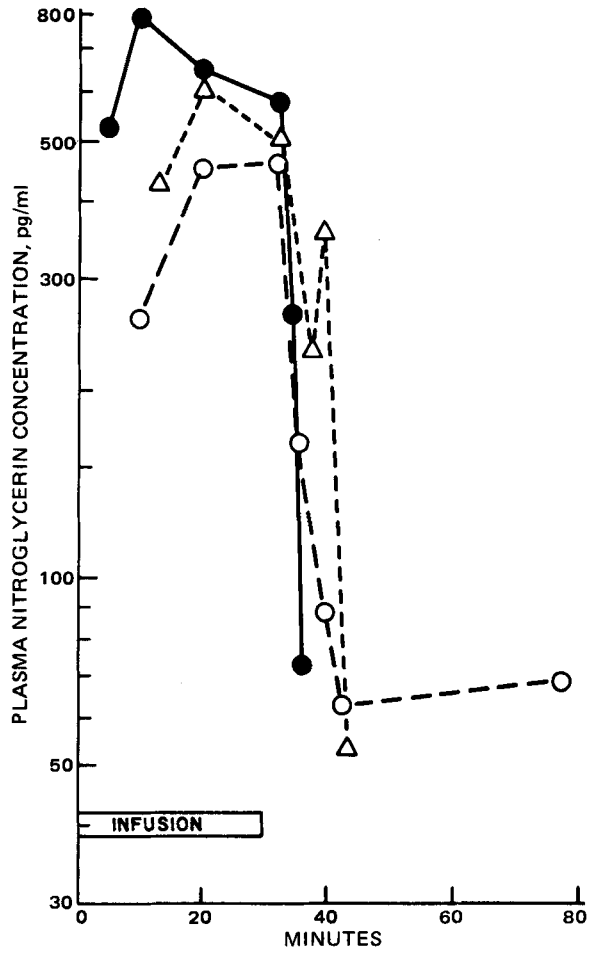

Figure 2—*Plasma nitroglycerin concentrations after intravenous administration to Subjects 5B (●), 7 (○), and 8 (△).*

Table II—Pharmacokinetic Data Obtained after Intravenous Nitroglycerin Infusion in Normal Subjects

Subject	Infusion Rate, μg/min	Dose, μg	K, min^{-1}	$t_{1/2}$, min	V_d, liters/kg	$Cl_s = \frac{D}{AUC}$, liters/min/kg	$Cl^* = \frac{k_0}{C_{32}}$, liter/min/kg	Apparent Steady State Achieved
5B	18.9	605	0.52	1.3	1.7	0.31 (29.8)[a]	0.33	Yes
7	16.4	524	0.21	3.3	2.4	0.49 (37.7)	0.43	Yes
8	16.5	527	0.19	3.7	2.9	0.54 (31.3)	0.57	Yes
3	18.6	596	0.25	2.8	4.1	1.02 (73.4)	0.67	No
4	15.5	496	0.18	3.8	5.2	0.94 (60.2)	0.66	No
5A	16.6	531	0.31	2.2	2.4	0.74 (71.0)	0.47	No
9	18.6	598	0.31	2.2	4.1	1.03 (78.3)	0.90	No
6	18.2	584	—	—	—	—	—	--
10	21.5	688	—	—	—	—	—	--
Mean	17.9	573	0.28	2.8	3.3	0.72 (54.5)	0.58	
±*SD*	1.8	59	0.12	0.9	1.2	0.28 (21.1)	0.19	

[a] Number in parentheses represents total body clearance (Cl_s × body weight), liters per minute.

of each sample concentration from the calculated infusion concentration was 2.8 and 4.1% for Runs 1 and 2, respectively.

Nitroglycerin concentrations in the infusion bottle, preinfusion, and postinfusion samples are shown in Table I. Analysis of variance (one way) showed that there was no statistical difference ($p > 0.35$) between these concentrations. Thus, the infusion system was apparently saturated with respect to adsorption, and the administered dose can be estimated from the infusion concentrations as described.

Subject 1 experienced nausea and fainting after the test sublingual doses were administered and was excused from the intravenous study. Subject 2 was not affected by the sublingual doses but was so nervous during the intravenous study that blood samples could not be easily withdrawn. No pharmacokinetic data were obtained from this subject.

Subjects 3–10 completed the study without any undesirable effects. Subject 5 was studied twice, separated by a period of 4 months. Intersubject variability in plasma nitroglycerin concentrations was quite large. Based on the shape of the plasma nitroglycerin concentration *versus* time profile, the data can be conveniently divided into three groups. Group A included three profiles (Fig. 2) in which steady-state nitroglycerin concentration was apparently achieved. Group B consisted of four profiles (Fig. 3) in which no steady state was apparent. Group C included two profiles (Fig. 4) in which plasma nitroglycerin concentrations were fluctuating erratically such that pharmacokinetic analysis was impossible.

Table II summarizes the individual data and the estimated pharmacokinetic parameters. The systemic clearance values were calculated according to both Eqs. 2 and 4. When an apparent steady state in plasma concentration was achieved during the infusion period, the two methods yielded essentially identical values. When an apparent steady state was not achieved, the value calculated by dose/AUC was always larger than that obtained by k_0/C_{32}. Irrespective of the calculation method, the systemic nitroglycerin clearance was extremely rapid (~0.3–1 liter/min/kg). The apparent volume of distribution at 3.3 liters/kg also was high. Since plasma volume is ~42 ml/kg (10), the apparent volume of distribution for nitroglycerin was ~80 times the plasma volume.

Except in Subjects 6 and 10, nitroglycerin elimination was rapid; an average half-life of ~3 min was observed. In several subjects, an apparent rebound in plasma nitroglycerin concentration occurred at ~15 min after the infusion was stopped (Figs. 2–4). Fortunately, this phenomenon occurred generally after the washout elimination phase had gone through two or three apparent half-lives. Thus, pharmacokinetic analysis of the remaining infusion data could be performed without these later time points.

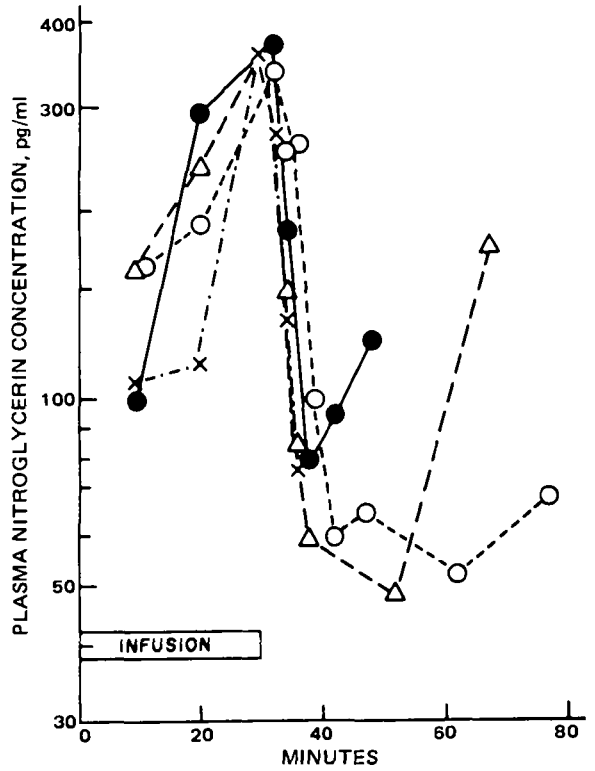

Figure 3—*Plasma nitroglycerin concentrations after intravenous administration to Subjects 3 (●), 4 (○), 5A (△), and 9 (×).*

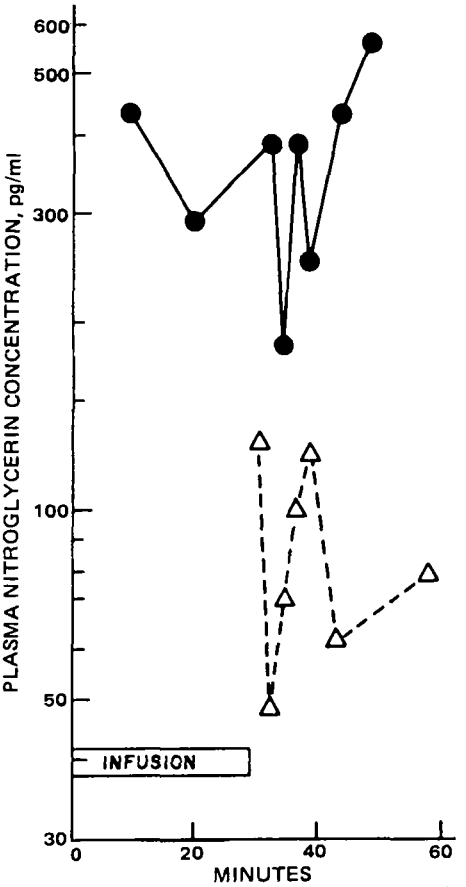

Figure 4—*Plasma nitroglycerin concentrations after intravenous administration to Subjects 6 (●) and 10 (△).*

Table III—Mean Heart Rate and Systolic and Diastolic Blood Pressure in Seven Normal Subjects [a] following Intravenous Infusion of 0.6 mg of Nitroglycerin during 30 min

Parameter	Mean	*SD*
Heart rate per minute		
Preinfusion, control	67.7	14.0
Postinfusion, maximum	75.4	14.9
Postinfusion, minimum	61.4	11.1
Systolic blood pressure, mm/Hg		
Preinfusion, control	117.1	20.6
Postinfusion, maximum	118.7	16.8
Postinfusion, minimum	106.0	15.3
Diastolic blood pressure, mm/Hg		
Preinfusion, control	76.6	10.4
Postinfusion, maximum	80.3	8.8
Postinfusion, minimum	72.6	9.3

[a] In two subjects, these parameters were monitored but not reported.

In the early part of this study, the cannula used for infusion was removed from the subjects as soon as possible. This step was taken ~15 min after cessation of the infusion. Initial data analysis suggested that removal of the cannula might be coincidental with the rebound in plasma drug concentrations. It was reasoned that manipulation of the cannula during removal might cause disturbance and release of tissue bound drug near the infusion site or of a small volume of infusion solution from the cannula into plasma, resulting in transient increases in plasma nitroglycerin concentrations. To test this hypothesis, Subject 5 was used again and Subjects 9 and 10 were studied without disturbing the infusion cannula during the entire postinfusion sampling period. Inspection of the respective plasma concentration profiles indicates that this procedure had no apparent effect. In fact, Subject 10 was one of the two subjects whose plasma kinetics showed the most fluctuation. In cases where the infusion cannula remained in place during the postinfusion sampling period, no postinfusion sample of the dosing solution was collected.

The dose infused (0.6 mg over 0.5 hr) did not produce any significant changes in heart rate or systolic and diastolic blood pressures in the subjects (Table III).

DISCUSSION

Plasma nitroglycerin kinetics are characterized by rapid disappearance and an apparently large plasma clearance. The plasma half-life of nitroglycerin determined from this study (2.8 ± 0.9 min, mean ± *SD*) is in good agreement with values reported by Armstrong *et al.* (2, 11) for arterial samples after intravenous administration (1.9 min) and after sublingual nitroglycerin dosing (4.4 min). Recently, these authors also reported (12) a half-life of *in vitro* nitroglycerin degradation in human blood of ~6 min at 37°. Therefore, *in vivo* blood (plasma) elimination of nitroglycerin is at least a result of both blood degradation and organ metabolism, the latter most probably by the liver (13).

The apparent plasma clearance determined in this study ranged from 0.31 to 1.03 liters/min/kg, corresponding to values of total body clearance of 29.8–78.3 liters/min. Although there are some methodological differences among this study and previous ones (1, 2), the apparent systemic clearance values determined from each of the three studies were all quite high (Table IV).

The data of Armstrong *et al.* (2) require some additional comments. These authors utilized arterial samples, and preliminary reports (14, 15) suggested that arterial nitroglycerin concentrations might be substantially higher than those found in peripheral veins. The somewhat lower systemic clearance values obtained by these authors are consistent with this suggestion. In addition, their patients were classified into two groups. Patients in Group 1 were generally responsive to hemodynamic management with nitroglycerin infusion, while those in Group 2 seemed to be refractory to nitroglycerin treatment. Group 1 patients received a lower infusion rate than patients in Group 2 (15–94 *versus* 59–440 μg/min, respectively) and showed higher ($p < 0.005$) systemic clearances (13.8 *versus* 3.6 liters/min, respectively). Based on the infusion rate, it is perhaps more appropriate to compare results from the normal subjects in the present study with those of Group 1 patients from the previous study.

Substantial intersubject variability in nitroglycerin kinetics was observed in the present study. The plasma nitroglycerin concentrations of Subjects 5B (second trial), 7, and 8 seemed to reach apparent steady state during the 32-min infusion. The good agreement obtained between Cl_s values calculated from Eqs. 2 and 4 confirmed that steady state was achieved. The average clearance from these three subjects was 0.45 liter/min/kg, which agreed well with a value of 28 liters/min (0.4 liter/min/kg assuming an average body weight of 70 kg) reported previously (11) following sublingual nitroglycerin administration.

In contrast, the plasma nitroglycerin concentrations of Subjects 3, 4, 5A (first trial), and 9 did not approach apparent steady-state values. In these cases, the clearance value estimated with the *AUC* was much larger than that calculated using k_0/C_{32} and also larger than that found with the first group. This result suggests that a significant portion of the area may be unaccounted for in these subjects. The estimated plasma half-lives in these subjects, however, were not dissimilar from those found with the first group, nor were they substantially different from values of 4.4 min reported after sublingual nitroglycerin (11) and of 1.9 min in arterial samples (2) after intravenous infusion. Nevertheless, a terminal disposition phase that is below the present limits of detection possibly may exist. The presence of a prolonged β-phase is consistent with the lack of attainment of steady-state plasma concentrations in these subjects. However, Subject 5 behaved differently in two separate trials: in the first trial (5A), steady state was achieved while in the second trial (5B), it was not. This information suggests that plasma nitroglycerin kinetics could vary substantially.

By using the apparent clearance values obtained, an apparent volume of distribution of 3.3 ± 1.2 liters/kg (mean ± *SD*) can be estimated. By using a plasma volume of 42 ml/kg (10), the amount of nitroglycerin residing in the plasma compartment can account for 1.3% of the total body load. Minor fluctuations in nitroglycerin content in the nonplasma (tissue) compartment, which may result from a host of internal and external stimuli, could cause dramatic fluctuations in plasma nitroglycerin concentrations. In Subjects 6 and 10, such wide fluctuations in plasma nitroglycerin concentrations occurred that no pharmacokinetic analysis was possible. Coincidentally, there was difficulty in placing the intravenous catheter in these two subjects. It is interesting to speculate that the release of endogenous substances after minor tissue damage may have some effect on the tissue distribution of nitroglycerin.

Although this study was not designed to examine the hemodynamic response to nitroglycerin infusion in detail, no significant change was observed in the monitored parameters. This finding is not surprising in view of the small doses and low infusion rates employed. In fact, nitroglycrin has been infused in normal subjects at rates as high as 200 μg/min with no significant adverse hemodynamic effect (16).

The observation of apparent rebound and oscillations in plasma nitrate concentrations in some subjects is not unique to this study. A similar phenomenon (17) was recently reported following intravenous infusion of isosorbide dinitrate. Because of its extensive tissue distribution, rapid plasma clearance of nitroglycerin during the postinfusion period may lead to a nonequilibrium redistribution of tissue drug back to the plasma compartment. The situation may be analogous to that observed for serum procainamide concentrations in patients immediately after hemodialysis (18). In that case, rebound and oscillations of procainamide concentra-

Table IV—Comparison of Study Methods and Pharmacokinetic Parameters Obtained among Three Investigations

	Wei and Reid (1)	Armstrong *et al.* (2)	Present
Subjects	Patients with acute myocardial infarction	Patients with congestive heart failure	Normal volunteers
n	5	16	8
Apparent infusion rate, μg/min	37.5–175	15–440	15–22
Blood sampling site	Vein (unspecified)	Radial artery	Antecubital vein
Calculated systemic clearance, liters/min	14–146	7.0–24.7[a] 0.9–6.4[b]	29.8–78.3
Mean elimination half-life, min	—	1.9	2.8

[a] Responsive group as defined in Ref. 2. [b] Nonresponsive group as defined in Ref. 2.

tions were attributed to shifts of drug into and out of various body compartments following drug clearance by hemodialysis (18).

Finally, the very large apparent plasma nitroglycerin clearance observed in this and other studies (1, 2) after intravenous administration warrants some comments. The apparent plasma clearance is not only greater than liver plasma flow but it also exceeds cardiac output. Physiologically, it is difficult to conceive how any drug can be cleared, in reality, faster than cardiac output. However, several possibilities might have led to the present experimental observation.

First, the dose actually infused into each subject was substantially less than that used in the pharmacokinetic calculation. For the apparent plasma nitroglycerin clearance to equal cardiac output [~7 liters/min for a 70-kg man at rest (19)], the dose infused would have to be ~10–25% of the dose used in calculation. This wide divergence in dose is considered unlikely because of the great care taken in the present study to minimize and account for drug adsorption in the infusion sets and because nitroglycerin concentrations emerging at the end of the infusion line were actually determined before and after infusion.

Second, there is substantial nitroglycerin degradation in the blood itself due to spontaneous hydrolysis or enzymatic breakdown. Armstrong *et al.* (12) gave a $t_{1/2}$ of 6 min for *in vitro* nitroglycerin degradation in human blood at 37°. If it can be assumed that this half-life reflects *in vivo* spontaneous blood degradation, the contribution of this process to the total apparent clearance will be $0.693/6 \times 69 \simeq 8.0$ ml/min/kg [using a blood volume of 69 ml/kg of body weight (10)], which is ~1% of the total apparent clearance (Table II). Even if the half-life of *in vivo* blood degradation is assumed to be equal to the systemic *in vivo* plasma half-life ($t_{1/2}$ = 3 min, Table II), the maximum contribution of spontaneous blood degradation to the apparent clearance will still be only ~2%.

Third, the *AUC* used in the calculation of clearance does not represent the total *AUC; i.e.*, a much longer secondary or tertiary plasma half-life exists but cannot be experimentally determined because of assay limitations. However, in the present study the plasma nitroglycerin concentrations in three subjects appeared to have reached steady state within the short infusion period of 15 min. In these subjects, a hidden and prolonged half-life probably does not exist.

Fourth, when the drug is infused into the systemic circulation, a first-pass removal process possibly may be present in the vascular bed so that the infused dose is not totally available to the systemic circulation. In other words, the vascular bed functions as a first-pass extraction tissue towards an intravenous dose of nitroglycerin in much the same way that the liver serves as a first-pass extraction organ for an oral dose. If this assumption is correct, then the apparent clearance values obtained will have to be corrected by an apparent bioavailability factor, which is less than unity. The demonstration of substantial differences in arterial *versus* venous nitroglycerin concentrations (14, 15) is not inconsistent with the hypothesis that blood vessels can clear nitroglycerin. Experiments conducted in rats (20) suggested that first-pass vessel uptake of nitroglycerin does occur. The apparent bioavailability factor, however, was not quantitated. The extent of the contribution of this phenomenon to the observed clearance value in humans also is unknown at present.

In conclusion, nitroglycerin kinetics in humans are characterized by apparent extensive tissue distribution and rapid plasma clearance. Because of these factors, plasma nitroglycerin concentrations may be subjected to high intra- and intersubject variabilities. This does not necessarily mean, however, that the effects produced by intravenous nitroglycerin also may be highly variable. Indeed, data from this laboratory (20) suggested that the presumed target tissue of nitroglycerin, the blood vessels, has a much higher concentration of drug compared to plasma. The systemic pharmacological effects of nitroglycerin may be better related to drug concentrations in the blood vessels than to those in plasma. Studies are in progress to characterize the pharmacokinetics of nitroglycerin in these presumed target tissues.

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