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STEADY STATE PHARMACOKINETIC HAEMODYNAMIC STUDIES OF INTRAVENOUS NITROGLYCERIN IN CONGESTIVE CARDIAC FAILURE

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1 We conducted pharmacokinetic haemodynamic studies in 10 patients with congestive cardiac failure to determine both the time to steady state concentration after commencement of a standard infusion rate of 21 μg/min i.v. GTN and the haemodynamic response once steady state plasma concentration was achieved.

2 Nitroglycerin was detected in plasma 2 min after commencement of the infusion, the concentration rose to a peak of approximately 4 ng/ml at 30 min and was maintained throughout the balance of the infusion period.

3 During GTN infusion heart rate, systolic blood pressure and cardiac index were unchanged; there was significant declines ($P < 0.01$) in pulmonary systolic pressure (SPA) (52 to 42 mm Hg), pulmonary capillary wedge pressure (PCWP) (26 to 20 mm Hg), and right atrial pressure (RAP) (12 to 8 mm Hg). These pressure changes were first evident within 5 min, approached maximum by 10 min and were maintained throughout the remainder of the infusion period.

4 A one compartment model fitted to haemodynamic and GTN data revealed time constants (± approximate standard error) for SPA, PCWP, RAP and GTN of 8.2 (3.4), 9.7 (3.0), 8.1 (3.8) and 8.1 (1.9 respectively. Clearance for GTN was 6.2 ± 2.7 (s.d.) l·min.

5 These data demonstrate steady state concentration of GTN is approached asymptotically with a time constant of 8.1 min during i.v. infusion of 21 μg/min. The time constants for haemodynamic measurement most sensitive to GTN's effect, i.e. SPA, PCW and RAP were remarkably similar to the time constant found for GTN concentration.

6 Although a 30 min period is required to achieve steady state GTN concentration our data confirm that for clinical use of i.v. GTN, titration of the infusion rate at 10 min intervals can be guided by the haemodynamic response.

Keywords i.v. nitroglycerin congestive cardiac failure

Introduction

The traditional therapeutic role of nitroglycerin (GTN) has recently been extended to a wide variety of clinical problems. Although several routes of administration are available for GTN and other nitrates, an intravenous infusion is particularly appropriate in the critically ill hospitalized patient (Cottrell & Turndorof, 1978). The increasing clinical use of GTN has stimulated vigorous investigation of its pharmacodynamics and kinetics in both normal and diseased states.

Limited information exists concerning the correlation between haemodynamic effects and plasma concentrations following intravenous nitroglycerin (i.v. GTN) (Wei & Reid, 1979). Our initial studies suggested that the therapeutic range for GTN in arterial plasma from patients with congestive cardiac failure was between 1.2 and 11.1 ng/ml (Armstrong *et al.*, 1980). We also observed that a wide variation in the plasma concentration was required to achieve haemodynamic changes and that despite very high concentrations some patients proved resistant. Following cessation of GTN infusion a short half-life of 1.9 min was determined. This short half-life, coupled with the observation that a haemodynamic steady state occurred within approximately 10–15 min of commencement of an i.v. GTN infusion, suggested to us that plateau plasma concentrations would also be achieved within 10–15 min. No data are available

however, in such patients to support this contention.

Accordingly in this study our objectives in patients with congestive cardiac failure were;

(1) to determine the time to steady state concentration after commencement of a standard infusion rate of 21 μg/min i.v. GTN,
(2) to assess the haemodynamic response at steady state plasma concentration.

Methods

Patient population

Ten patients with congestive cardiac failure formed the study group: there were five males and five females ranging in age from 57 to 68 years. Three patients were insulin-dependent diabetics. Seven patients had coronary artery disease as the basis for their heart failure: in two, heart failure complicated a recent myocardial infarction and in five, it was chronic and had been established for at least 3 months. The three remaining patients in the study group had chronic congestive cardiomyopathy. All eight patients with chronic congestive cardiac failure were in functional class 3 or 4 and refractory to conventional therapy including digoxin and frusemide. All patients had radiographic documentation of heart failure as defined by cardiomegaly and pulmonary venous congestion and confirmed by control haemodynamics (Table 1).

After informed consent was obtained, patients were instrumented in a standardized fashion for haemodynamic monitoring. This included placement of a Swan Ganz thermodilution catheter in the pulmonary artery and a teflon cannula in the radial artery. Right atrial (RAP), pulmonary arterial and pulmonary capillary wedge pressures (PCWP) obtained by balloon occlusion, as well as systemic arterial pressure, were monitored. Cardiac output was measured at least in duplicate by thermodilution with injection of 10 ml of ice cold 5% dextrose and water into the right atrium (Forrester *et al.*, 1972). After a control period of 20–30 min during which haemodynamic measurements were shown to be reproducible, i.v. GTN was infused at a rate of 21 μg/min in the arm contralateral to the radial artery cannula for 120 min.

Constant physiological monitoring was performed throughout the infusion period, and pressure measurements were obtained at 2, 5, 10, 15, 30, 60 and 120 min after commencement of the infusion, with cardiac output measured at all but the 2 min point. If PCWP was not reduced by at least 25% of its control value during the 120 min infusion of GTN, the infusion was increased in step-wise fashion every 10–15 min: this continued until this haemodynamic endpoint had been achieved or a greater than tenfold increment in the initial infusion rate had been attained. The haemodynamic endpoint was achieved in all patients except subjects 2, 5 and 10; accordingly they received incremental GTN infusions. These latter three subjects all had chronic congestive failure but were not distinguishable from the other patients in the group with respect to aetiology of heart disease or baseline haemodynamics.

Derived haemodynamic calculations were performed using the formula:

$$CI = \frac{CO}{BSA}$$

where CI = cardiac index in l min^{-1} m^{-2}, CO = cardiac output in l/min, BSA = body surface area in m^2.

Arterial samples for plasma nitroglycerin determination were withdrawn during the control period and at the points where pressure measurements were recorded during the 120 min infusion at 21 μg/min. Additional samples were withdrawn after at least 30 min at the peak infusion rate in those patients in whom the haemodynamic endpoint was not achieved with 21 μg/min i.v. GTN.

Blood samples were immediately centrifuged at 5°C and the decanted plasma was frozen at −20°C. Subsequent analysis was performed using gas-liquid chromatography with dinitrobenzene as the internal standard according to a method previously described (Armstrong *et al.*, 1982). GTN 1 ng/ml is equivalent to 4.4 nmol/l.

GTN (Nitrostat i.v. 0.8 ng/ml Warner-Lambert Co., Ann Arbour, Michigan) was prepared in glass bottles of 5% dextrose solution so as to achieve a final concentration of 100 μg/ml. The GTN solution was delivered from 50 ml glass syringes using a Harvard infusion pump and teflon connecting tubing which does not adsorb GTN (Armstrong *et al.*, 1982). The concentration of GTN in the original stock solution was verified using g.l.c. analysis.

Clearance for GTN was calculated in two ways in this study;

(i) using the formula

$$\text{clearance} = \frac{\text{infusion rate}}{\text{concentration}}$$ (Greenblatt & Koch-Weser, 1975)

where infusion rate = 21 μg/min; however in this calculation concentration = the average GTN concentration in each patient at 30, 60 and 120 min points during the infusion.

(ii) using the formula

$$\text{clearance} = \frac{\text{infusion rate}}{C_{ss}}$$

where infusion rate = 21 μg/min and C_{ss} = steady state concentration determined by nonlinear regression analysis.

In addition to nonlinear regression analyses, the data were analyzed using correlation analysis and analysis of variance where appropriate.

Results

The haemodynamic response to 21 μg/min i.v. GTN over the 120 min infusion period, along with the accompanying GTN concentrations for all 10 patients, i.e. seven responders and three non-responders, are shown in Table 1. Nitroglycerin was determined in plasma 2 min after commencement of the infusion and the concentration rose to a peak of approximately 4 ng/ml at 30 min: this concentration was maintained throughout the balance of the infusion period. During the GTN infusion there was no change in heart rate, systolic blood pressure (SBP) or CI, but there was a significant decline in pulmonary artery systolic pressure (SPA), PCWP and RAP. These pressure changes were first evident within 5 min, approached maximum by 10 min, and were maintained throughout the remainder of the infusion period.

The time course of the changes in PCWP and plasma GTN concentrations during the 120 min infusion period is shown in Figure 1. GTN concentration rose progressively during the first 15 min, reached a peak concentration at 30 min and was maintained near that level throughout the remainder of this study. A prompt fall was seen in PCWP after the commencement of infusion with the maximum effect observed at 10 min and this was sustained throughout the 120 min period.

Since several haemodynamic variables *viz* SPA, PCWP, RAP and the GTN concentration approached steady state values asymptotically at apparently similar rates we reasoned that a one compartment model would fit the data. Accordingly, a model of the form

$$y = C_p + A_p (1 - e^{-t B})$$

was fitted to the haemodynamic responses using non-linear regression analysis. In the model, C_p represents the control value for a patient, A_p represents the steady state change in the response for that patient, and B is a common time constant parameter for all patients. Using this model we obtained a time constant (± approximate standard error) for SPA, PCWP and RAP of 8.2 (3.4), 9.7 (3.0) and 8.1 (3.8) respectively.

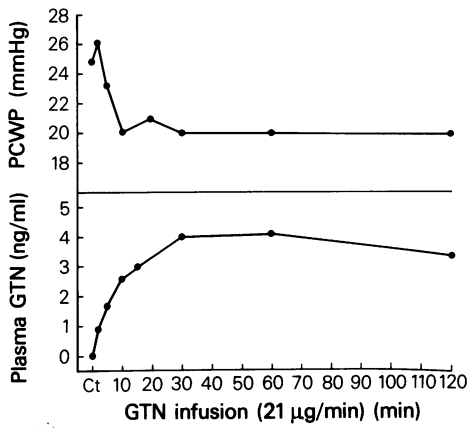

Figure 1 Time course of changes in pulmonary capillary wedge pressure (PCWP) (upper panel) and plasma GTN concentration (lower panel) during the 120 min GTN infusion.

Table 1 Summary of haemodynamic response to 21 μg/min i.v. GTN (n = 10)

		Time (min)							
	Control	*2*	*5*	*10*	*15*	*30*	*60*	*120*	*Pooled s.d.*
HR	95 ± 18	94	95	90	94	93	93	92	7
SBP	127 ± 22	130	129	126	127	127	130	129	22
SPA	52 ± 6	52	46	46	45	42	41	45	6
PCWP	25 ± 4	26	23	20	21	20	20	20	4
RAP	12 ± 2	12	10	9	10	8	9	8	2
CI	1.9 ± 0.5	—	2.1	2.2	2.2	2.2	2.2	2.2	0.3
GTN	0	0.9	1.7	2.6	3.0	4.0	4.1	3.4	1.7

HR = heart rate in beats/min, SBP = systolic blood pressure,
SPA = systolic pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure, RAP = right atrial pressure (all pressures in mm Hg),
CI = cardiac index in l min^{-1} m^{-2}.
GTN = plasma nitroglycerin concentration in ng/ml.
Pooled s.d. is derived from 1 way ANOVA of the differences from control values. All data represent means: s.d. are shown for control values.
The changes in SPA, PCWP and RAP are significant $P < 0.01$ (2 way ANOVA).

A one compartment model was also fitted to the nitroglycerin concentration data in the form

$$y = C_{ss}(1 - e^{-t/B})$$

using nonlinear regression analysis. In this model, C_{ss} is the steady state concentration, B is the time constant parameter and t is time in minutes. Using the data from all patients, we obtained estimates of C_{ss} = 3.65 ng/ml (s.e. mean 0.9) and B = 8.1 min (s.e. mean 1.9). At elapse of time equal to one time constant, the concentration of GTN reaches 69% of the steady state value, or 2.5 ng/ml, which is extremely close to the average GTN concentration of 2.6 (s.d. 1.5) ng/ml determined at 10 min after the beginning of i.v. GTN infusion.

A comparison of time constant parameter estimates for plasma GTN and the haemodynamic responses noted previously demonstrates remarkable similarity. Analysis of the correlation between these haemodynamic changes from control and plasma GTN demonstrated no relationship for SPA and a weak but statistically significant relationship for PCWP and RAP ($r = -0.45$ and -0.40, $P < 0.001$).

Clearance calculated using average GTN values at 30, 60 and 120 min to determine C revealed a clearance value of 6.2 ± 2.7 (s.d.) l/min. When clearance was calculated using C_{ss} derived from nonlinear fitting we found a similar clearance of 21/3.65 = 5.75 l/min (approx s.e. mean 1.4).

In three of the 10 patients we failed to reach the haemodynamic endpoint of at least a 25% fall in PCWP. One of these patients showed a decline from 30 to 25 mm Hg in PCWP at a much higher infusion rate of 220 μg/min and had no change in RAP. In the other two patients, although there was no change in PCWP, RAP fell by at least 25% during the 21 μg/min infusion suggesting that a relatively selective pharmacological effect had been achieved. In Figure 2a the haemodynamic response of one of these individuals is shown over the initial 120 min infusion period with the corresponding plasma GTN levels: there was no change in PCWP but RAP fell from 20 to 15 mm Hg. As shown in Figure 2b increments in the infusion rate produced an increase in plasma GTN concentration from 2.0 ng/ml at 21 μg/min to greater than 70 ng/ml at 160 μg/min. This rise in GTN concentration resulted in a progressive decline in PCWP to 15 mm Hg and a slight fall in RAP. Thirty minutes after cessation of the 160 min infusion at 160 μg/min, haemodynamic parameters had partially returned to control.

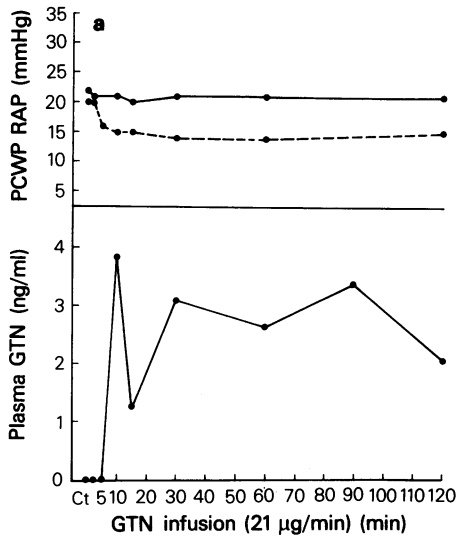

Figure 2a Individual response of patient failing to reach haemodynamic endpoint during infusion of 21 μg min GTN. No change is seen in pulmonary capillary wedge pressure (PCWP, ●——●) and right atrial pressure (RAP, ●- -●) falls from 20 to 15 mm Hg.

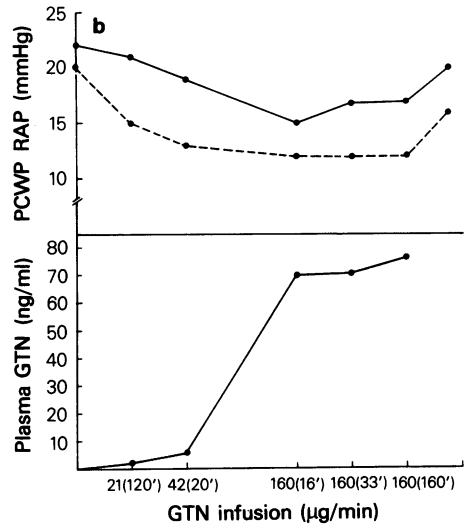

Figure 2b Influence of increasing GTN infusion rate on haemodynamic parameters (pulmonary capillary wedge-pressure, PCWP (●——●) and right atrial pressure, RAP (●- -●), and plasma GTN concentration of the same patient as in Figure 2a. The final haemodynamic data points were taken 30 min after cessation of the GTN infusion.

In Figure 3, a patient with a good initial haemodynamic response is shown. The effects were most pronounced between 30 and 60 min after infusion of GTN and were associated with a plasma GTN concentration of 6 ng/ml. During the final phase of GTN infusion PCWP returned to control values unexpectedly. Subsequent analysis of plasma GTN revealed that the GTN concentration had fallen to 1 ng/ml at this time. These data suggest that there had

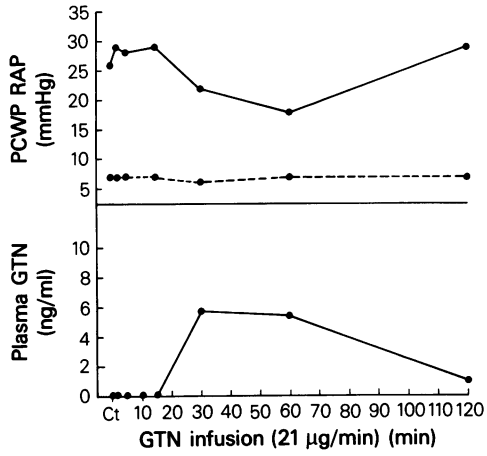

Figure 3 Patient response in individual with favourable change in pulmonary capillary wedge pressure (PCWP, ●——●) during initial phase of GTN infusion. Return to control PCWP and fall in plasma GTN at 120 min suggests undetected problem in GTN delivery. Upper panel ●--● right atrial pressure (RAP).

been an undetected problem with GTN delivery during the study.

Discussion

This study demonstrates that a steady state concentration of nitroglycerin is approached asymptotically with a time constant of 8.1 min during i.v. infusion of 21 μg/min GTN. Classic pharmacokinetic analysis indicates that true steady state is not achieved until 4–5 time constants have elapsed; the value of 8.1 min suggests that steady state should have been achieved by 30–40 min (Greenblatt & Koch Weser, 1975). This prediction fits our data well since as shown in Figure 1, a steady state value of 4.0 ng/ml was observed 30 min after commencement of the infusion.

We did not systematically evaluate the elimination $t_{½}$ in our patients. However, in two subjects who had received higher infusion rates of GTN, $t_{½}$ values of 2.8 and 1.1 min were determined and these are consistent with our previously reported value of 1.9 min (Armstrong *et al.*, 1980). In earlier studies we estimated the time to haemodynamic steady state of GTN following i.v. infusion to be 15 min. From this information, coupled with the short $t_{½}$ of 1.9 min, we expected a pharmacokinetic steady state at 10–15 min. The current study shows that this is not the case and indicates that samples taken prior to 30 min underestimate true steady state concentration. It is of interest that arterial GTN plasma concentrations in this study are somewhat higher than those we have reported in man at comparable infusion rates. This finding may relate to the fact that sampling in our previous studies occurred at variable times and often before true kinetic steady state had been achieved.

Although the arterial clearance for GTN calculated in this study (6.2 ± 2.7 l/min) was significantly lower than we have previously reported in patients with heart failure (13.9 ± 8.7 l/min) ($P < 0.01$) it was within the same range (Armstrong *et al.*, 1982). For purposes of comparison with the present study patients with GTN arterial concentrations in the same range (i.e patients 1–14) were used. The lower value for clearance in the current study likely relates to the fact that all patients received the same infusion rate of 21 μg/min for a standard period of 120 min, whereas in our previous study the infusion rate of GTN varied from 15 to 82 μg/min and extended over variable time periods. Less interpatient variability was observed in the clearance calculations in the present study. This diminished variability was expected since the concentrations of all patients were at steady state and that three separate plasma samples were used in the clearance calculation whereas a single plasma sample was used in the previous study.

It is of interest to consider our data in the light of the recent report by McNiff and colleagues (1981). These workers studied the pharmacokinetics of intravenous GTN in the peripheral venous blood of eight normal subjects during 18 μg/min (average) infusion for 32 min. They found low (< 1 ng/ml) and variable GTN concentrations and observed that steady state was achieved in only three of their subjects. The differences from their data and ours likely are accounted for by several factors:

(1) Study length: The time at which their GTN infusion was terminated was nearly identical to the time taken for us to achieve steady state concentration for GTN in the current study, raising the question as to whether McNiff and co-workers (1981) would have found more uniform concentrations had they sampled for a longer time.

(2) The circulatory sampling site: GTN concentration was determined in venous blood in their study and in arterial blood in ours. We have previously shown a 60% extraction for GTN between arteries and veins; whether the time to steady state in venous blood is the same as in arterial blood is uncertain.

(3) Magnitude of measured concentration: The concentration in their study was much lower, i.e. ≤ 0.8 ng/ml *vs* 4 ng/ml. These lower concentrations may be more sensitive to variability with haemodynamic perturbations than higher ones.

We have previously demonstrated that PCWP and RAP are the most sensitive haemodynamic indicators of GTN's effect in cardiac failure. In this study there was a weak but significant linear relationship between changes from control for PCWP and RAP and GTN concentration. The time constants for haemodynamic

measurements most responsive to GTN's effect, i.e. SPA, PCWP, and RAP were remarkably similar to the time constant found for GTN concentration. Despite the similarities in time constants it should be noted that the major change in PCWP and RAP had occurred 10 min after commencement of the infusion. Although a 30 min period is required to achieve steady state GTN concentrations our data confirm that for the clinical use of i.v. GTN titration of the infusion rate at 10 min intervals can be appropriately guided by the haemodynamic response.

Questions remain regarding the persisting effect of nitrates and the issue of tolerance formation. No tolerance was evident during this study (120 min) as indicated by maintenance of the haemodynamic effect through the duration of the infusion, and return towards control haemodynamics after cessation of GTN infusion (Figure 2b). The importance of GTN measurement during investigative studies is highlighted in Figure 3. Had we relied exclusively on haemodynamic or other bioassay determinations of the effect of GTN in this instance we would have surmised that the effectiveness of the drug had diminished with time (Smolen, 1980). Instead, the measurement of GTN identified that a fall in concentration had occurred and was likely secondary to an undetected delivery problem.

Resistance to GTN was observed in three patients in the present study. Earlier studies from our institution have shown diminished response to high doses of GTN in some patients which was not selective but also demonstrable with nitroprusside (Armstrong *et al.*, 1978). The mechanism for resistance in patients with congestive cardiac failure is unclear. Marked peripheral oedema, indistensibility of the peripheral vasculature and high systemic vascular resistance mediated by neuroendocrine responses in heart failure have been implicated (Magrini & Niarchos, 1980; Cohn *et al.*, 1981). These factors were not predictive of haemodynamic response in our patients. Better discrimination of patient response to vasodilator therapy in congestive cardiac failure may be possible with characterization of the neurohumoral aspects of heart failure such as circulating catecholamines, serum renin and arginine vasopressin (Cohn *et al.*, 1981).

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