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Haemodynamics and plasma concentrations following sublingual GTN and intravenous, or inhaled, isosorbide dinitrate

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1 We measured plasma nitrate levels and haemodynamics following sublingual glyceryl trinitrate (GTN) (0.5 mg), or isosorbide dinitrate (ISDN) administered intravenously (0.5 mg) or by inhalation (1.25 mg) in 23 patients undergoing cardiac catheterisation for investigation of chest pain.

2 Peak levels were detected at 90 s and 5 min following intravenous and inhaled ISDN respectively and at 3 min following sublingual GTN.

3 Intravenous and inhaled ISDN produced similar plasma levels at 30 s and both were significantly greater than following sublingual GTN.

4 Plasma levels were maintained for longer following inhaled ISDN than intravenous ISDN or sublingual GTN.

5 Haemodynamic responses were qualitatively similar following each treatment; reduction in pulmonary vascular resistance and pressure and left ventricular end diastolic pressure occurred in each group. Heart rate, cardiac output and LV $dP/dt.P^{-1}$ remained unchanged.

6 Maximal haemodynamic responses were greater following ISDN than GTN, with little difference between the two preparations of ISDN.

7 Haemodynamic responses were more sustained following inhaled ISDN than following sublingual GTN or intravenous ISDN, the latter two being similar in this respect.

8 These findings suggest that inhaled ISDN may provide more rapid and sustained relief from angina than sublingual GTN.

Keywords nitrates pharmacokinetics haemodynamics

Introduction

Sublingual glyceryl trinitrate (GTN) remains the most widely used agent for rapid relief of angina pectoris. Slow release oral nitroglycerin preparations provide a more prolonged effect but are limited by rapid hepatic transformation (Goldstein *et al.*, 1971; Needleman *et al.*, 1972). Oral isosorbide dinitrate (ISDN) has also been shown to have a sustained action (Williams *et al.*, 1977; Franciosa *et al.*, 1974), and to improve exercise tolerance following acute (Kasparian *et al.*, 1975; Glancy *et al.*, 1977) and chronic treatment (Danahy & Aronow, 1977; Lee *et al.*, 1978; Thadani *et al.*, 1980). Inhalation of ISDN has the theoretical advantage of allowing direct absorption into the systemic circulation and thereby of providing a rapid onset of action and sustained effect. To investigate this we compared haemodynamic responses and plasma levels following sublingual GTN, inhaled ISDN and intravenous ISDN. A preliminary account of this work has been presented previously (Culling *et al.*, 1983).

Methods

Studies were carried out in 23 male patients undergoing cardiac catheterisation for investiga-

tion of chest pain after obtaining informed consent. Ethical approval for the study was obtained from our hospital ethical committee. Clinical details are summarised in Table 1. Long acting nitrates were discontinued for 24 h prior to study but sublingual GTN was freely available. In order to standardise β-adrenoceptor blocking treatment all patients were given atenolol 100 mg twice daily for 24 h prior to study, their own β-adrenoceptor blocking therapy being discontinued temporarily. Patients were fasted for 12 h prior to study and received diazepam 10 mg orally as premedication. Heart rate was measured from ECGs as the mean of 6 beats. A size 7 French catheter tip transducer, inserted percutaneously was used to record left ventricular pressure and the signal differentiated using analogue circuitry (Siemens) to derive dP/dt and $dP/dt.P^{-1}$. A separate fluid filled catheter was used to record femoral artery pressure (Statham pressure transducer). Cardiac output was measured in duplicate by thermodilution (Instrumentation Labs.) using a flow directed thermodilution catheter advanced to the pulmonary artery from the left basilic vein. The latter was also used to record pulmonary artery pressure. Following control observations each patient received sublingual GTN (0.5 mg), or ISDN given intravenously (0.5 mg) or by inhalation (1.25 mg). The latter was administered using an aerosol spray cartridge fitted with a metering valve (Cedocard spray, Pharma-Schwartz). Repeat measurements were obtained at 0.5, 1.5, 5, 15, and 30 min thereafter. Blood samples were taken as close as possible to each series of haemodynamic recordings for measurement of drug levels. An additional sample was obtained at 60 min following inhaled ISDN.

Blood samples for GTN and ISDN assays were collected in heparinised glass tubes containing 50 μl 0. In silver nitrate to prevent *in vitro* metabolism (Yap *et al.*, 1980). Extraction and assay of GTN was as previously described (Bashir *et al.*, 1983). The lower limit of GTN detection was 0.2 ng/ml, and the intra-assay coefficient of variation for GTN concentrations of 0.5–5 ng/ml was 10.7% ($n = 6$). The mean percentage recoveries for concentrations between 0.5–5 ng/ml was 82.2 ± 1.6% (s.e. mean, $n = 6$). For ISDN estimations blood samples were immediately centrifuged at 400 *g* for 15 min at 40°C. Plasma (3 ml) was transferred to 20 ml glass tubes and mixed with 10 μl of 7.5 ng/ml γ-lindane acting as internal standard, and 10 ml of double distilled petroleum spirit (boiling point 40–60°C) was added. The mixture was shaken for 15 min in a flat bed shaker, and the two phases separated by centrifugation at 400 *g* for 5 min at 4°C. The upper organic layer was transferred to a conical glass tube and the petroleum spirit was evaporated gently under a stream of air to near dryness. The residue was dissolved in 100 μl of ethyl acetate and the samples were kept at −20°C until chromatography.

A g.l.c. apparatus (Pye-Unicam, UK Model 104) supplied with an electron capture detector (ECD) containing 10 mCi Ni^{63} as the radioactive source was used. The glass columns (150 cm long and 2.4 mm internal diameter) were packed with 3.5% w/w QF2 on a gas Chrom Q support (60–90 mesh). New columns were conditioned at 140°C with nitrogen as carrier gas at a flow rate of 65 ml/min for 36 h prior to use. The operating conditions were as follows: column oven temperature 140°C; detector oven temperature 250°C; carrier (nitrogen) gas flow rate of 65 ml/min. The rubber septum of the injection port was changed every 20 injections. At the end of each experimental day the detector oven temperature was raised at 350°C to clean the ECD overnight. ISDN was assayed using γ-lindane as internal standard and a new standard curve was constructed each day by plotting the ratios of the peak heights of the γ-lindane and ISDN chromatograms against the ISDN concentrations. The retention times were: ethylacetate 35 s, γ-lindane 349 s, and ISDN 542 s. The lower limit of detection for ISDN was 0.2 ng/ml. The coefficient of linear regression for the calibration curves was 0.97–0.99. The intra-assay coefficient of variation was 8.17% for 0.5–10 ng/ml. The mean percentage recovery for concentrations 0.5–10 ng/ml was 83.7 ± 3.6%.

Comparisons within each treatment group were made using Student's paired *t*-test and between groups using Student's non paired *t*-test.

Results

Patients within each group were well matched for age and treatment prior to study (Table 1). Twenty patients (87%) had at least one vessel disease, determined by coronary angiography immediately following the haemodynamic study. The incidence of coronary artery disease was similar in each group (Table 1), although severe disease (two or more vessels involved) was fortuitously less in the group which received intravenous ISDN (38%), than those given sublingual GTN (50%) or inhaled ISDN (86%).

Plasma concentrations

Plasma concentrations for each drug are illustrated in Figure 1. The peak level occurred

Table 1 Clinical details

Treatment studied	*Group 1 sublingual GTN*	*Group 2 i.v. ISDN*	*Group 3 inhaled ISDN*	*Total*
Number	7	8	8	23
Age (years ± s.e. mean)	49.9 ± 1.9	50.9 ± 3.2	49.8 ± 2.4	50.2 ± 1.5
Previous therapy				
β-adrenoceptor blocker	6	8	6	20
Chronic oral nitrates	6	6	8	20
Calcium antagonists	3	2	2	7
Severity of heart disease				
Previous myocardial infarction	5	3	6	14
Area of segmental LV hypokinosis	4	4	6	14
Extent of coronary disease				
No C.A.D.	1	2	0	3
1 vessel	0	3	3	6
2 vessel	4	1	1	6
3 vessel	2	2	4	8

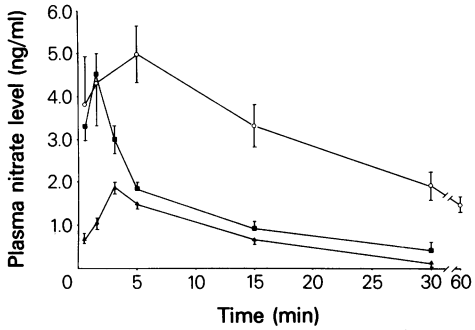

Figure 1 Plasma levels following intravenous (0.5 mg, ■), or inhaled (1.25 mg, O) isosorbide dinitrate, or sublingual glyceryl trinitrate (GTN. ▲). Results are given as the mean ± s.e. mean.

earliest following intravenous administration. Although the peak level did not occur until 5 min following inhalation of ISDN, the level obtained at 30 s indicates rapid absorption, and it is of interest that plasma concentrations were similar at this time following intravenous administration and inhalation of the drug. While plasma levels increased between 1.5 and 5 min following inhalation of ISDN, a sharp fall (probably reflecting dilution of the drug) occurred after 1.5 min following intravenous administration, plasma concentrations remaining higher thereafter in the former ($P < 0.05$). The peak plasma level was significantly less following sublingual GTN than intravenous or inhaled ISDN ($P < 0.05$); however there was little difference between levels following sublingual GTN and intravenous ISDN after 5 min (Figure 1). At 30 min plasma levels were significantly higher in the group given inhaled ISDN than those who received intravenous ISDN or sublingual GTN ($P < 0.05$). Pharmacologically significant levels were also detected 60 min following inhalation (Figure 1).

The haemodynamic responses observed with each preparation are illustrated in Figures 2, 3, 4 and 5. Control haemodynamics were similar in each group with the exception of left ventricular end diastolic pressure which was higher in patients who received inhaled ISDN (13.6 ± 2.8) or sublingual GTN (13 ± 1.9) than those given intravenous ISDN (5.5 ± 1.2 mm Hg). This is likely to reflect the lower incidence of severe coronary artery disease in the latter group. For comparative purposes changes in left ventricular end diastolic pressure were expressed as percent of control.

Heart rate and cardiac output

As illustrated in Figure 2, no significant changes in heart rate, or cardiac output were observed in response to any of the preparations studied.

Blood pressure

Changes in pulmonary and arterial pressure are illustrated in Figure 3. Mean pulmonary pressure was significantly reduced in each group. The onset of this effect was more rapid following intravenous and inhaled ISDN than sublingual GTN. Thus pulmonary pressure was significantly reduced at 90 s in the former but remained unchanged in the latter. The duration of this effect

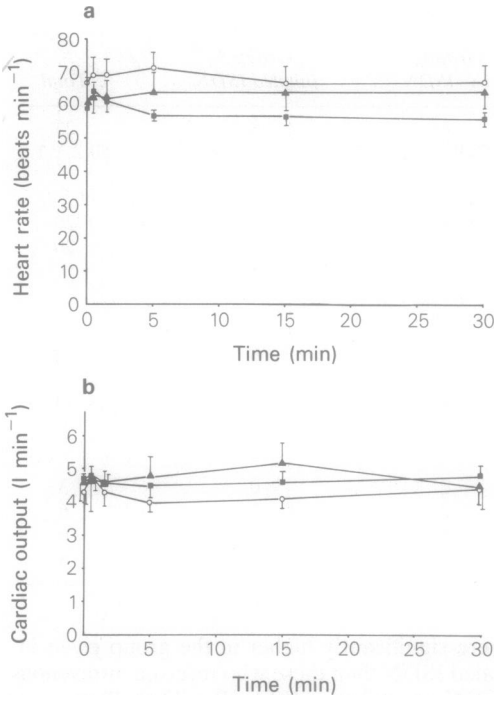

Figure 2 Heart rate (a) and cardiac output (b) prior to and following intravenous (■) or inhaled (○) isosorbide dinitrate, or sublingual GTN (▲). Results are expressed as mean ± s.e. mean.

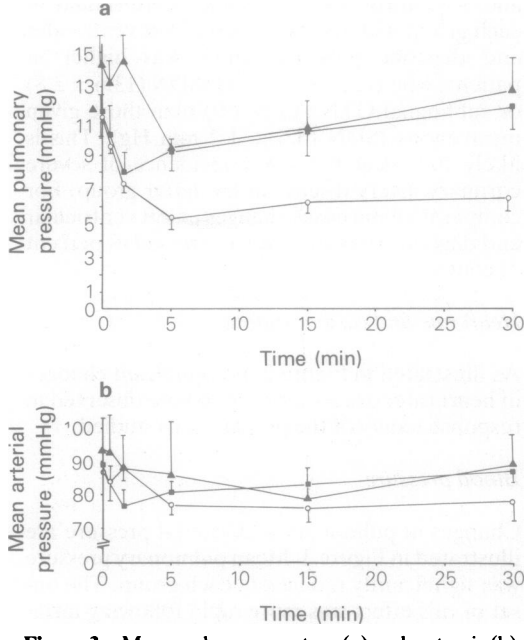

Figure 3 Mean pulmonary artery (a) and systemic (b) pressures (mean ± s.e. mean) prior to and following intravenous (■) or inhaled (○) isosorbide dinitrate, or sublingual GTN (▲).

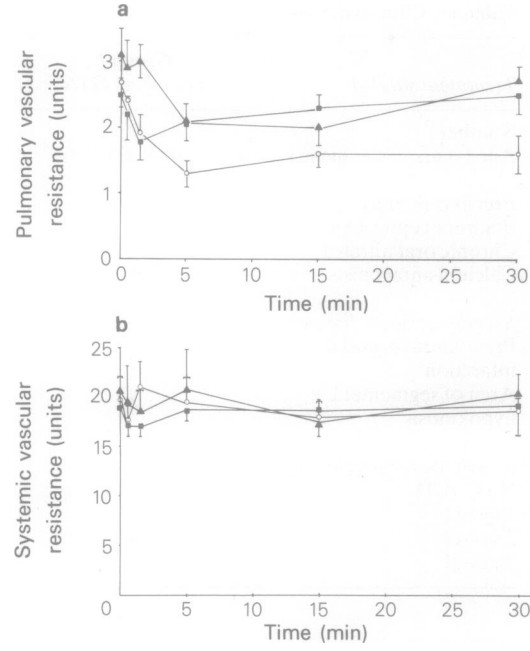

Figure 4 Changes in pulmonary (a) and systemic (b) vascular resistance (mean ± s.e. mean) following intravenous (■) or inhaled (○) isosorbide dinitrate, or sublingual GTN (▲).

was longest in the group which received inhaled ISDN. Thus at 30 min mean pulmonary pressure remained significantly reduced in this group but had returned to control values in those who received sublingual GTN or intravenous ISDN. Mean systemic pressure was also reduced in each group. Although these changes did not reach statistical significance, the time course was similar to that for pulmonary pressure. Thus onset was slowest in the group which received sublingual GTN and lasted longest in the group which received inhaled ISDN.

Pulmonary and systemic vascular resistances

Changes in pulmonary and systemic vascular resistances are illustrated in Figure 4. Pulmonary vascular resistance was significantly reduced in each group ($P < 0.05$). The onset of these changes was more rapid following intravenous or inhaled ISDN than following sublingual GTN and the effect was longer lasting following inhaled ISDN. Thus pulmonary vascular resistance was significantly reduced at 90 s following intravenous or inhaled ISDN but remained unchanged following sublingual GTN, and this effect was maintained at 30 min following inhaled ISDN but not following sublingual GTN or intravenous ISDN. An initial transient reduction in systemic vascular

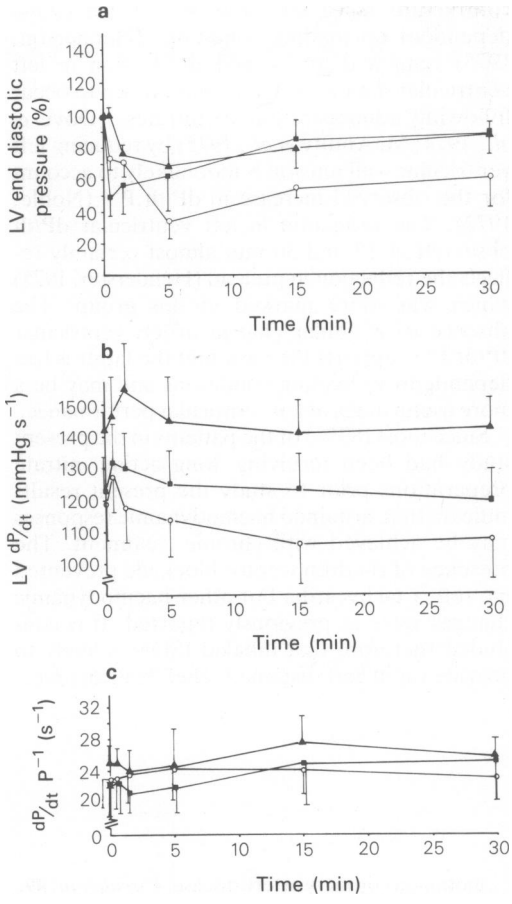

Figure 5 Changes in left ventricular end diastolic pressure (a) left ventricular dP/dt (b) and left ventricular $dP/dt.P^{-1}$ (c) following intravenous (■) or inhaled (○) isosorbide dinitrate, or sublingual GTN (▲). Results are expressed as mean ± s.e. mean.

resistance was observed in each group, however none of these changes reached statistical significance.

Left ventricular end diastolic pressure

Changes in left ventricular end diastolic pressure are illustrated in Figure 5. Significant reductions in left ventricular end diastolic pressure were observed in each group. The peak effect occurred at 30 s following intravenous ISDN, and at 5 min following sublingual GTN and inhaled ISDN. The onset of action was more rapid following inhaled ISDN than sublingual GTN. Thus a significant effect was observed at 30 s following the former but not the latter. The changes observed were maintained for longer following inhaled ISDN than sublingual GTN or intravenous ISDN.

Left ventricular indices of contractility

Left ventricular dP/dt and $dP/dt.P^{-1}$ are illustrated in Figure 5. A transient increase in left ventricular dP/dt lasting 1.5 to 5 min was observed in each group, but never reached statistical significance. Thereafter little change occurred except in patients given oral spray ISDN who showed a significant decrease at 15 and 30 min ($P < 0.05$). These findings were not accompanied by similar changes in left ventricular $dP/dt.P^{-1}$ (Figure 5).

The duration of haemodynamic effects corresponded closely with the plasma levels observed, being greatest following inhaled ISDN. Thus, pulmonary vascular resistance and pressure and left ventricular end diastolic pressure has returned to control at 30 min following sublingual GTN and intravenous ISDN, but remained significantly reduced ($P < 0.05$) following inhalation of ISDN (Figures 3, 4 and 5).

Discussion

This study demonstrates that prompt absorption of ISDN occurs following inhalation. The associated haemodynamic changes occur more rapidly than following sublingual GTN and are only slightly less rapid than following intravenous ISDN, but are sustained for longer than either of the latter. The doses of each drug were chosen to allow comparison of those likely to be used in practice. It is possible that the higher dose of inhaled ISDN used may have contributed to the longer duration of action; however this would not explain the more rapid onset of action than sublingual GTN. It is likely therefore that inhaled ISDN may provide more rapid and sustained relief of angina than sublingual GTN. Although the mechanism by which nitrates relax smooth muscle remains unclear their haemodynamic effects are well known (Mason & Braunwald, 1965; Horschen *et al.*, 1966; Mason *et al.*, 1971; DeMaria *et al.*, 1974). The changes observed in this study were qualitatively similar following each preparation, being a reduction in pulmonary vascular resistance and left ventricular filling pressure. A reflex posture dependent tachycardia is also frequently observed in response to GTN treatment (Ross *et al.*, 1981). Its absence in the present study is likely to reflect the presence of β-adrenoceptor blockade.

There is general agreement that nitrates reduce pulmonary vascular resistance and dilate systemic veins, thereby reducing left ventricular filling pressure (Mason & Braunwald, 1965; Horschen *et al.*, 1966; Mason *et al.*, 1971; DeMaria *et al.*,

1974; Brachfeld *et al.*, 1959). The effect of nitrates on systemic vascular resistance is less clear. Nitroglycerin has been reported to reduce forearm vascular resistance (Mason & Braunwald, 1965), and some workers have demonstrated a reduction in total systemic vascular resistance (Brachfeld *et al.*, 1959), while others have not (DeMaria *et al.*, 1974; Brachfeld *et al.*, 1959; Armstrong *et al.*, 1980). In the present study a small reduction in systemic vascular resistance was observed in each group; this initial reduction was followed by a further rise and fall in patients given sublingual nitroglycerin and inhaled ISDN. The mechanism for this oscillation in systemic vascular resistance is not clear. It may reflect reflex vasoconstriction in response to a reduction in mean arterial pressure, overcoming the direct vasodilating action of the drug, an effect which would be accentuated by the presence of β-adrenoceptor blockade.

Previous studies have demonstrated an improvement in left ventricular wall motion in response to GTN (Dove *et al.*, 1974; McAnulty *et al.*, 1975). In the present study left ventricular dP/dt was transiently increased by each preparation. The mechanism for this is unclear. It is unlikely to reflect a change in left ventricular contractility since LV $dP/dt.P^{-1}$, which is less dependent on loading conditions (Henderson, 1975) remained unchanged. Reduction in left ventricular dimensions, which is known to occur following administration of nitrates, (Dove *et al.*, 1974; McAnulty *et al.*, 1975) by reducing left ventricular wall tension is more likely to account for the observed increase in $dP/dt.P^{-1}$ (Noble, 1972). The reduction in left ventricular dP/dt observed at 15 and 30 min almost certainly reflects the reduction in preload (Henderson, 1975) which was more marked in this group. The absence of a similar change in left ventricular $dP/dt.P^{-1}$ supports the view that the latter is less dependent on loading conditions and may be a more useful index of left ventricular performance.

Since most (87%) of the patients in the present study had been receiving 'long acting' nitrate preparations prior to study the present results indicate that sustained haemodynamic responses may be achieved with chronic treatment. The presence of β-adrenoceptor blockade prevented the reflex tachycardia but other haemodynamic changes were as previously reported. It is concluded therefore that inhaled ISDN is likely to provide rapid and sustained relief from angina.

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