Haemodynamic dose-response effects of i.v. nicardipine in coronary artery disease

B. SILKE, S. P. VERMA, G. I. C. NELSON, M. HUSSAIN & S. H. TAYLOR

University Department of Cardiovascular Studies and Department of Medical Cardiology, The General Infirmary, Leeds

1 The haemodynamic dose-response effects of the slow channel blocking agent nicardipine were evaluated in 10 male patients with angiographically confirmed coronary artery disease. At rest, following a similar control saline period, four doses of the drug (log cumulative dosage: 1.25, 2.5, 5.0 and 10.0 mg) were administered by i.v. infusion over a total duration of 40 min; haemodynamic variables were recorded in the 3-5 min following each 5 min infusion. During steady-state exercise the haemodynamic effects of the drug were evaluated by comparison of a control exercise period with observations made at the same workload (200-500 kpm) following the maximum cumulative dose (10 mg).

2 Following the four i.v. infusions, the plasma nicardipine level increased log-linearly with the infused dose ($r = 0.68$). Compared with control measurements at rest after saline, these plasma concentrations (35 ± 8 to $141 \pm 24 \mu\text{g/l}$) resulted in a linear decrease in systemic blood pressure and vascular resistance with significant increase in cardiac index (maximum $\Delta\text{CI} + 1.6 \text{ l min}^{-1} \text{ m}^{-2}$; $P < 0.01$), stroke index (maximum $\Delta\text{SI} + 11 \text{ ml/m}^2$; $P < 0.01$) and in pulmonary artery occluded pressure (maximum $\Delta\text{PAOP} + 2 \text{ mm Hg}$; $P < 0.01$). There was a significant increase in heart rate; the stroke work index was unchanged.

3 During upright bicycle exercise the reduction in systemic blood pressure was accompanied by an increased exercise cardiac output without change in stroke index. The exercise pulmonary artery occluded pressure was unchanged compared with control observations, the stroke work index fell significantly ($P < 0.05$).

4 The changes in resting haemodynamic variables following nicardipine reflect the influence of a reduction in left ventricular afterload favourably modifying cardiac performance in ischaemic heart disease. During exercise, with near maximal vasodilatation, the additional reduction in systemic vascular resistance on nicardipine did not further improve exercise haemodynamics. However, nicardipine, over a wide intravenous dose-range, did not result in undue depression of cardiac function; thus it would appear to be haemodynamically safe, even in relatively severe coronary artery disease.

Keywords nicardipine coronary artery disease dose-response haemodynamics

Introduction

Drugs which retard the intracellular migration of ionic calcium are of proven value in the therapy of cardiovascular disease (Dargie *et*

al., 1981; Winniford *et al.*, 1982). The slow calcium channel blocking agents are not homogenous having differing structural, electro-

physiological and pharmacological properties (Henry, 1980). Their impact on cardiac performance is complex, being the resultant of the relative affinities of each compound for vascular smooth or cardiac muscle; calcium channel blockers which act predominantly on vascular smooth muscle reduce left ventricular afterload with little impairment of cardiac pumping function, whereas agents with both peripheral and marked central effects reduce cardiac performance to a greater extent (Kieval *et al.*, 1982; Ahuja *et al.*, 1983; Nelson *et al.*, 1984).

Nicardipine is a newer slow-calcium channel blocking agent; animal data have suggested relative specificity for vascular smooth muscle with little cardiodepressant action (Schiantarelli *et al.*, 1982). In this regard, its affinity for smooth muscle is more specific than nifedipine (Schiantarelli *et al.*, 1982) or diltiazem (Baisch *et al.*, 1982), but nicardipine has equivalent effects in augmenting coronary blood flow (Hof, 1983). Preliminary studies have confirmed its vasodilator action (Seki & Takenaka, 1977) and its antihypertensive (Taylor *et al.*, 1982) and anti-anginal (Bala-Subramanian, 1982) efficacy; volunteer data have demonstrated improved indices of cardiac performance following its acute administration (Iliopoulou *et al.*, 1983; Campbell *et al.*, 1984). The following study was an evaluation of the resting haemodynamic dose-response effects following nicardipine infusion in patients with reproducible angina pectoris together with analysis of the effects of the drug on left ventricular performance during upright bicycle exercise.

Methods

Patients

Ten males, aged 31–57 years (mean 47 ± 2) with uncomplicated chronic stable angina pectoris (average duration 16 ± 6 months, range 4–60) were studied during diagnostic evaluation prior to coronary artery bypass grafting. All had angiographically confirmed coronary artery disease (single vessel in four, double vessel in one and triple vessel in five); four had a previous myocardial infarction > 6 months prior to these studies (three inferior; one anterior). None had radiographic evidence of left ventricular failure at rest (cardiothoracic ratio 0.48 ± 0.1). The angiographically calculated ejection fraction was $50 \pm 7\%$ (range 22–72%). Left ventricular angiography demonstrated an inferior wall scar in two and an area of anteroapical dyskinesia in a further two

patients. Resting left ventricular wall motion in the remaining six patients was normal. In all subjects the exercise workload (predetermined on two occasions for each patient during a training session) reliably induced angina between 2–4 min of upright bicycle exercise. The average workload was 400 ± 34 kpm (range 200–500). No patient had crescendo angina, nor was hypertensive nor diabetic. All patients were in sinus rhythm; none had previously received sustained cardioactive therapy other than short acting nitrates; none required any medication in the 12 h preceding the study. Informed consent was given by all patients and investigation was approved by the hospital Ethics Committee.

Design of investigation (Figure 1)

The study was designed as a single-blind placebo-controlled within-patient dose-response evaluation of intravenous nicardipine. Patients were studied fasting without premedication. Patients were familiarised on two occasions prior to the definitive procedure with the laboratory surroundings and the maximum workload which each could maintain for 4 min, without intolerable symptoms was determined. The variability in haemodynamic variables following this training period has been previously determined; during 3 repeated exercise tests at > 20 min intervals (i.e. recovery time) the variance for systolic and diastolic blood pressure, heart rate, cardiac output and PAOP was 3.3%, 4.1%, 2.9%, 5.9% and 14.5% respectively (Verma *et al.*, 1983). The study commenced with a 4 min period of upright bicycle exercise, load limited to the pre-determined individual angina threshold; circulatory measurements were made minute by minute. Haemodynamic variables were allowed to restabilise (20 min); resting measurements were then made during eight consecutive 4 min periods with the patient sitting quietly at rest in a comfortable chair. The first four periods followed 10 ml control saline infusion over 2 min, haemodynamic variables being recorded in the last 2 min of each 4 min control period; the second 4 each followed 5 min nicardipine infusion (1.25, 1.25, 2.5 and 5 mg); haemodynamic measurements being determined in the 8–10 min of each drug period. The dosage schedule was designed to give logarithmically cumulative doses of 1.25, 2.5, 5.0 and 10.0 mg. These doses of nicardipine were based on the results of a preliminary non-invasive dose-ranging study; they are somewhat lower than the doses assessed in volunteers (Iliopoulou *et al.*, 1983; Campbell *et al.*, 1984).

Figure 1 Study design. ▨ haemodynamic measurements.

Venous blood samples were taken for measurement of plasma nicardipine concentration at the time of haemodynamic measurements (3–5 min following cessation of each infusion). At the end of the resting studies patients were re-exercised for 4 min at the same bicycle workload as in the control study; measurements were again recorded minute by minute.

Laboratory techniques, measurements and statistics

Heart rate was measured from electrocardiogram (CM5) and systemic arterial pressure through a brachial artery catheter. Pulmonary vascular pressures were measured through a balloon-tipped thermodilution catheter (7F; Gould Inc. SP 5107) positioned radiographically so that inflation of the balloon resulted in replacement of the pulmonary artery pressure record by a typical pulmonary wedge tracing (pulmonary artery occluded pressure—PAOP). Pressures were externally transduced with strain gauges (zero reference being at mid-chest level) and recorded together with heart rate (EMI 6300). Mean pressures were integrated electronically and heart rate and pressures were averaged over at least two respiratory cycles. Cardiac output at rest was measured in triplicate by thermodilution and automatically computed (Gould Statham SP 1435 Computer/SP 2009 Recorder). During steady-state bicycle exercise duplicate determinations were recorded at 1 min intervals. A gas-operated constant speed injector (OMP Model 3700) was used with 10 ml of dextrose saline at 0°C as indicator. When evaluated in our laboratory this system was linear *in vitro*; its variance was determined during the diagnostic catheterisation of 24 patients. In each of 12 subjects, 10 consecutive resting thermal dilution cardiac outputs were recorded at 1 min intervals; the variance averaged 5.4% (range 2.3–7.8%). In each of a further 12 subjects studied during 6

min steady state bicycle exercise, 10 consecutive thermal dilution estimates in each subject demonstrated an average variance of 6.5% (range 2.3–11.3%). Systemic and pulmonary vascular resistance, stroke volume and left ventricular stroke work were calculated according to conventional formulae and corrected for body surface area as follows:

$$\text{systemic vascular resistance} = \frac{\text{mean systemic artery pressure (MAP)}}{\text{cardiac output}} \times 80$$

$$\text{stroke volume (SV)} = \frac{\text{cardiac output}}{\text{heart rate}}$$

$$\text{left ventricular stroke work} = \text{SV} \times (\text{MAP} - \text{PAOP}) \times 0.0136$$

The ejection fraction was measured blind from the average of three planimetric integrations of the LV angiogram performed in the right anterior oblique projection. The average variability of this technique was less than 5%. Coronary artery obstruction was defined as narrowing of > 70% in any of the major coronary vessels.

Plasma nicardipine concentration was determined using a specific high performance liquid chromatographic technique with ultra-violet detection (254 nm). The assay was linear over the measured range with a coefficient of variation of less than 10%; the lower limit of sensitivity was 2 µg/l. Statistical analysis of the dose-response studies at rest involved two procedures. The probability of statistical significance of differences between control and post-drug data was tested by analysis of variance of repeated measurements (Dixon & Brown, 1979). Tukey's Studentised Range Test (Winer, 1971) was then used to generate the single value by which difference between drug and control values was tested. Trends were tested by fitting analysis of variance curves to the means. Variation of measurements during the control

studies was determined by the coefficient of variation and expressed as a percentage of the mean.

Results

The studies were completed without untoward incident in any patient. None complained of symptoms and none developed undue hypotension, heart block or excessive leg fatigue during exercise after the drug. Angina was induced in all subjects in the control exercise period; seven of the patients volunteered that severity of perceived angina was less during the second exercise study after nicardipine; in the remaining three anginal symptoms were unchanged.

Haemodynamic profile before nicardipine

During the control sitting period with repeated saline injections, the averages of the coefficient of variation were: systolic blood pressure 1.3% (range 0.7–2.8%); diastolic blood pressure 1.5% (range 0.9–2.3%); heart rate 3.1% (range 1.4–7.9%); cardiac output 3.3% (1.8–6.5%); pulmonary artery occluded pressure 8.0% (range 3.5–12.3%).

Upright bicycle exercise at constant speed and load was associated with significant increases in all measured haemodynamic variables which were maximum at the second minute of exercise and remained relatively unchanged for the rest of the 4 min exercise period. The calculated systemic vascular resistance was significantly reduced to a maximum by the second minute of exercise.

Nicardipine dose-response concentration relationship

There was a log linear relationship between the plasma nicardipine concentration achieved and the infused dose ($r = 0.68$; $P < 0.01$). The average plasma concentrations achieved, at the end of each drug period was 35 ± 8 , 47 ± 6 , 88 ± 3 and $141 \pm 24 \mu\text{g/l}$ respectively.

Haemodynamic changes induced by nicardipine (Figure 2)

At rest the cumulative doubling doses of intravenous nicardipine were associated with linear dose-related reduction in the systemic arterial systolic ($P < 0.05$), diastolic ($P < 0.01$) and mean pressure ($P < 0.01$). There were linear

increases in cardiac output ($P < 0.01$) and PAOP ($P < 0.01$) with a significant rise in heart rate ($P < 0.01$). There was a significant linear increase in stroke volume ($P < 0.01$) without change in stroke work index. The systemic vascular resistance showed a linear decrease (control 3035 ± 136 ; 10 mg cumulative dose $1610 \pm 88 \text{ dyn.s cm}^{-5} \text{ m}^{-2}$; $P < 0.01$).

Haemodynamic studies during exercise (Table 1)

During exercise following the 10 mg cumulative i.v. dose of nicardipine, there were reductions in the absolute levels of systemic arterial diastolic and mean pressures ($P < 0.01$) at each minute of exercise. The heart rate rose significantly ($P < 0.01$) and there was an increase in the cardiac output response to exercise ($P < 0.05$) without change in the stroke volume. The absolute level of the exercise pulmonary artery occluded pressure was unchanged. The systemic vascular resistance during exercise was significantly lower than that during the control study ($P < 0.01$); the calculated stroke work index during exercise was reduced ($P < 0.05$).

Effects of nicardipine on cardiac function (Figure 3)

The cardiac performance curve (i.e. cardiac output vs pulmonary artery occluded pressure) following the 10 mg nicardipine dose showed a significant improvement in these patients at rest. The curve was displaced upwards and to the right due to a significant rise in the cardiac output with a small increase in PAOP. During steady-state exercise the curve was displaced upwards due to an increased cardiac output at an unchanged PAOP.

Discussion

This study described the haemodynamic dose-response effects of intravenous nicardipine in patients with symptomatic coronary artery disease. Before discussing the results of the present study, the validity and limitations of the experimental design must be considered. A period of control exercise is usually followed by a period of relative haemodynamic stability (Taylor, 1965); this was demonstrated to have been present prior to the drug studies by the relatively small coefficient of variation of the haemodynamic variables over the saline period.

Figure 2 Haemodynamic dose-response effects (mean $\pm$ s.e. mean) of nicardipine infusion in 10 patients with coronary artery disease studied in the upright posture. Statistics relate to comparison with control. * $P < 0.05$, ** $P < 0.01$.

Figure 3 Effect (mean $\pm$ s.e. mean) of cumulative 10 mg nicardipine on cardiac function in coronary artery disease. * $P < 0.05$, ** $P < 0.01$.

Following control observations, four short intravenous nicardipine infusions were administered at 10 min intervals with evaluation of haemodynamic dose-response effects in the 8–10 min following commencement of each intravenous infusion. Pharmacokinetic studies in our laboratory in similar patients have indicated the half-life of distribution following intravenous nicardipine infusion to be between 2–3 min, thus the haemodynamic measurements were undertaken at a time by which substantial pharmacodynamic activity was likely to be present. The increase in plasma nicardipine concentration correlated log-linearly with the infused dose; over the plasma range achieved (35 to 141 $\mu g/l$) the linear decrease in diastolic and mean blood pressure directly reflected the dose-response effects on these circulatory variables.

In our patients with severe but clinically stable obstructive coronary heart disease, the effects of nicardipine were haemodynamically clear. The drug induced a reduction in systemic vascular resistance and blood pressure; the resultant reduction in left ventricular afterload was associated with significant increases in

Table 1 Haemodynamic effects of nicardipine in angina during upright bicycle exercise

		Rest	Exercise (min)			
			1	2	3	4
Systolic blood pressure (mm Hg)	Control	135 ± 6	160 ± 8	172 ± 8	176 ± 8	179 ± 8
	Nicardipine	129 ± 8*	157 ± 7	167 ± 7	170 ± 7	172 ± 7
Diastolic blood pressure (mm Hg)	Control	83 ± 4	88 ± 4	89 ± 4	89 ± 3	90 ± 4
	Nicardipine	65 ± 3**	79 ± 2**	81 ± 3**	81 ± 2**	82 ± 3**
Mean blood pressure (mm Hg)	Control	101 ± 5	112 ± 5	115 ± 5	119 ± 5	119 ± 5
	Nicardipine	84 ± 4**	101 ± 4**	106 ± 4**	107 ± 4**	107 ± 4**
Heart rate (beats/min)	Control	84 ± 4	115 ± 7	122 ± 7	124 ± 7	126 ± 8
	Nicardipine	99 ± 4**	126 ± 7**	135 ± 6**	139 ± 6**	141 ± 7**
Pulmonary artery occluded pressure (mm Hg)	Control	3 ± 1	8 ± 1	8 ± 1	9 ± 2	9 ± 1
	Nicardipine	5 ± 1**	8 ± 1	8 ± 1	9 ± 1	9 ± 1
Cardiac index (l min ⁻¹ m ⁻²)	Control	2.7 ± 0.2	5.1 ± 0.3	5.7 ± 0.3	6.0 ± 0.3	6.0 ± 0.4
	Nicardipine	4.3 ± 0.3**	5.7 ± 0.3*	6.2 ± 0.3*	6.3 ± 0.3	6.5 ± 0.3*
Systemic vascular resistance (dyn s cm ⁻⁵ m ⁻²)	Control	3035 ± 136	1786 ± 91	1648 ± 75	1610 ± 71	1626 ± 78
	Nicardipine	1610 ± 88**	1448 ± 66**	1378 ± 52**	1374 ± 61**	1338 ± 59**
Stroke volume (ml m ⁻²)	Control	33 ± 2	46 ± 3	47 ± 3	49 ± 3	48 ± 3
	Nicardipine	44 ± 3**	46 ± 3	47 ± 3	46 ± 3	47 ± 3

Data presented as mean ± s.e. mean
Statistics related to comparison with control **P* < 0.05, ***P* < 0.01.

cardiac output and stroke volume. However, the expected reduction in cardiac work, due to the reduction in left ventricular afterload consequent on systemic vasodilatation, was offset to some extent by the reflex sympathetically mediated tachycardia. Interestingly the fall in systemic blood pressure was partially compensated by the substantial increase in cardiac output; the diastolic blood pressure decreased to a greater extent than the systolic and as a result the pulse pressure widened. During 4 min steady-state upright bicycle exercise, the small additional decrease in systemic vascular resistance produced by nicardipine, compared with the control exercise value, did not further augment exercise cardiac stroke volume although the left ventricular stroke work index was significantly decreased.

These observations suggest that in the intact circulation nicardipine appears to act predominantly on the peripheral arteriolar bed, the reduction in left ventricular afterload allows improved cardiac pumping activity. Direct evidence of cardiac depression following nicardipine was not observed, however, the dose-related increase in resting pulmonary artery occluded pressure could be the consequence of such negative inotropic activity. Alternatively, the reflex sympathetic activation (Amlie *et al.*, 1978) due to systemic hypotension would itself be expected to decrease left ventricular compliance, accounting for at least some of the observed rise. However, the relative contributions of such direct and reflex effects in an integrated circulatory response can only be determined in the experimental model.

Our observations are compatible with volunteer studies with intravenous nicardipine which

demonstrated somewhat lesser hypotensive effects but improved indices of cardiac performance (Iliopoulou *et al.*, 1983). These pharmacodynamic findings have been recently confirmed in another non-invasive assessment of the drug (Campbell *et al.*, 1984). Taken together these data on nicardipine confirm circulatory actions which may be therapeutically advantageous in angina pectoris; the utility of the drug in attenuating anginal symptoms needs detailed evaluation (Bala Subramanian, 1982). The decrease in systemic blood pressure and sympathetic activation observed in the present study suggest that the addition of a β -adrenoceptor blocking drug to nicardipine to counter such reflex effects ought to be considered. The use of concurrent slow-calcium and β -adrenoceptor blockade in angina pectoris has been advocated (Ekelund & Oro, 1979; Lynch *et al.*, 1980; Tweddel *et al.*, 1981); the haemodynamic safety of concurrent nifedipine and metoprolol has recently been demonstrated (Pfisterer *et al.*, 1982; Nelson *et al.*, 1984). Pending more definite studies, our observations suggest that the drug nicardipine predominantly induces peripheral vasodilatation without undue evidence of cardiac depression in the intact circulation; it would appear to be haemodynamically well-tolerated even in patients with severe coronary artery disease.

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