Comparison of the haemodynamic profiles of elgodipine and nicardipine in the anaesthetized dog

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1 The haemodynamic profile of elgodipine ($1\text{--}30\text{ }\mu\text{g kg}^{-1}$, i.v.), a new dihydropyridine calcium antagonist, has been compared directly with that of nicardipine ($1\text{--}30\text{ }\mu\text{g kg}^{-1}$, i.v.) in chloralose-anaesthetized dogs.

2 Nicardipine produced dose-related systemic, pulmonary and coronary vasodilatation accompanied by reflex tachycardia, inotropy and increases in cardiac output and myocardial oxygen consumption (MVO_2). Elgodipine had similar vasodilator and hypotensive properties to nicardipine but produced less reflex inotropy, little or no reflex tachycardia and did not increase MVO_2 .

3 Both calcium antagonists were retested in a separate group of anaesthetized dogs pretreated with propranolol (1 mg kg^{-1} , i.v.) and atropine (0.3 mg kg^{-1} , i.v.) to abolish reflex autonomic tone to the heart and thus reveal the direct cardiac effects of each compound. Under these conditions both elgodipine and nicardipine decreased heart rate and cardiac contractility and slowed atrio-ventricular conduction. Elgodipine was approximately ten times more potent than nicardipine as a decelerator agent and slightly more potent in depressing cardiac contractility and increasing PR interval duration. Elgodipine, unlike nicardipine, slightly reduced the QTc interval of the electrocardiogram. Therefore, the potent decelerator effect of elgodipine, which was present throughout the dose-range, appears to be largely responsible for the suppression of reflex tachycardia observed when the baroreflex is functional.

4 Elgodipine is a potent systemic and coronary vasodilator with more marked direct cardiac effects than nicardipine, particularly with respect to slowing of heart rate. The ability of elgodipine to increase coronary blood flow without significant reflex tachycardia or increases in MVO_2 suggests that this compound will have a more favourable effect on myocardial oxygen supply/demand balance than nicardipine. The haemodynamic profile of elgodipine may be suitable for the treatment of angina.

Keywords: Elgodipine; nicardipine; dihydropyridine calcium antagonists; reflex tachycardia; vascular/cardiac selectivity; anaesthetized dog

Introduction

The success of the prototype calcium antagonists, nifedipine, verapamil and diltiazem in the treatment of a range of cardiovascular disorders has generated much interest in this mechanistic approach and has resulted in the development of a number of newer agents from the same drug class. This research for optimised calcium antagonists has focussed largely on variations in tissue selectivity profile and pharmacokinetic properties. Elgodipine is a recent example of the dihydropyridine structural family of calcium antagonists (Tamargo *et al.*, 1991) which demonstrates potent coronary dilator properties in the anaesthetized pig without significant depression of cardiac contractility (Sassen *et al.*, 1990). An account of the beneficial effects of elgodipine in patients with coronary artery disease has recently been published (Suryapranata *et al.*, 1992).

We have performed a detailed haemodynamic study of elgodipine in the anaesthetized dog. In order to strengthen the interpretation of the data obtained with elgodipine we have made direct comparison (in the same animals) with nicardipine, an established and clinically proven dihydropyridine calcium antagonist. Our objectives were, firstly, to identify similarities and differences between the two agents, and secondly, to evaluate the extent to which the haemodynamic profile of elgodipine appears appropriate for the treatment of angina or congestive heart failure. Angina is a traditional market for calcium antagonists and their efficacy, based on coronary vasodilator properties, is well accepted. However, occasionally, when used as monotherapy, the dihydropyridine calcium antagonists have been reported to cause paradoxical pro-ischaemic responses in patients with

coronary artery disease (Lambert *et al.*, 1985; HINT Research Group, 1986; Gheorghiade *et al.*, 1989). The reasons for such adverse responses are still the subject of discussion, but possible explanations include excessive hypotension causing simultaneous coronary hypoperfusion and reflex tachycardia (which increases oxygen demand), or the phenomenon of coronary steal (Waters, 1991). In contrast, calcium antagonists are not yet established in the treatment of congestive heart failure, largely due to concerns about their potential for cardiac depression as a result of direct negative inotropic properties (Packer, 1989). Hence the interest in agents which appear to be highly vascular selective.

In performing this study we have chosen a chloralose-anaesthetized dog model (Humphries & O'Connor, 1988) which allows the calcium antagonists to be evaluated under two different experimental conditions. Firstly, in 'normal' anaesthetized animals in which baroreceptor reflexes are still functional, such that systemic vasodilatation results in reflex cardiac stimulation (inotropy and chronotropy) as has previously been demonstrated to occur in anaesthetized dogs maintained on chloralose (O'Connor *et al.*, 1982; Humphries & O'Connor, 1988). Subsequently, to test the effects of elgodipine and nicardipine in a second group of otherwise similar animals in which efferent vagal and sympathetic cardiac tone were abolished by pharmacological intervention. This latter series of experiments enables an evaluation of the direct cardiac properties of each compound, uncomplicated by reflex changes in cardiac function. The extrapolation to man of haemodynamic data obtained in anaesthetized animals requires caution. By including a reference agent of known clinical profile (nicardipine) and by controlling the level of function of cardiac reflexes, which in anaesthetized

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animals can vary considerably according to choice of anaesthetic and species, we have attempted to design a study which avoids some of the obvious pitfalls.

Methods

Surgical preparation

Twelve beagle dogs of either sex (13–17 kg) were anaesthetized initially with sodium thiopentone (20 mg kg⁻¹, i.v.) a short-acting barbiturate and anaesthesia maintained throughout the experiment with α -chloralose (80 mg kg⁻¹, i.v. + 20–30 mg kg⁻¹ h⁻¹, i.v.). After tracheal intubation, the animals were artificially ventilated (Braun respiratory pump) with ambient air enriched with oxygen such as to maintain blood gas parameters (PO_2 , PCO_2 , pH) within normal limits.

A catheter was introduced into the right brachial artery and advanced into the thoracic aorta for measurement of arterial blood pressure. The anaesthetic infusion and administration of drugs was effected via catheters placed in left brachial and right femoral veins, respectively. A left thoracotomy was performed at the level of the fourth intercostal space and electromagnetic flow probes positioned around the ascending aorta and the circumflex coronary artery to measure aortic blood flow (cardiac output) and coronary blood flow, respectively. A catheter was placed in the pulmonary artery to measure pulmonary arterial pressure and another positioned in the left atrium to measure left atrial pressure. Left ventricular pressure was measured with a transducer-tipped catheter (Millar Instruments) introduced into the left ventricle via the right femoral artery. In order to preserve baroreceptor function, no catheterization was performed in the carotid vascular beds. The electrocardiogram (ECG, Lead II) was recorded continuously using subcutaneous needle electrodes.

Parameters measured

Aortic, pulmonary and left atrial pressures were measured with Gould Statham transducers connected to Hellige pre-amplifiers. The first derivative of left ventricular pressure (dP/dt) was obtained using a differentiator and dP/dt_{max} was used as the index of myocardial contractility. Aortic and coronary blood flows were recorded continuously with electromagnetic flowmeters (Carolina Medical Electronics) and the corresponding total peripheral and coronary vascular resistances were calculated by dividing mean arterial pressure by mean blood flow. Pulmonary vascular resistance was calculated by dividing mean pulmonary arterial pressure (following subtraction of mean left atrial pressure) by cardiac output. An indirect index of myocardial oxygen consumption (MVO_2) was calculated according to the formula of Rooke & Feigl (1982) shown below:

$$MVO_2 = 4.08 \times 10^{-4} (SBP \times HR) + 3.25 \times 10^{-4} \frac{(0.8SBP + 0.2DBP) \times HR \times SV}{BW} + 1.43$$

where SBP = systolic blood pressure (mmHg), HR = heart rate (beats min⁻¹), DBP = diastolic blood pressure (mmHg), SV = stroke volume (ml beats⁻¹) and BW = body weight (kg).

Left ventricular end diastolic pressure (LVEDP) was measured with a Millar transducer and heart rate measured from the ECG signal as were PR interval (an index of atrio-ventricular conduction time) and QTc interval (an index of ventricular repolarization time) the latter being corrected for changes in heart rate by use of the formula of Bazett (1920).

Experimental protocol

Animals were randomised in two experimental groups. In the first group ($n = 6$), the effects of elgodipine and nicardipine were investigated without any pretreatment. In the second group ($n = 6$), in order to study the effects of the compounds in the absence of cardiac reflexes, dogs were pretreated with propranolol (1 mg kg⁻¹, i.v.) and methylatropine (0.3 mg kg⁻¹, i.v.) to block cardiac sympathetic and vagal tones, respectively.

Each animal received bolus i.v. doses (1, 3, 10, 30 μ g kg⁻¹) of elgodipine (E_1 , E_3 , E_{10} , E_{30}) and nicardipine (N_1 , N_3 , N_{10} , N_{30}). In each experimental group the order of administration of bolus doses was: E_1 , N_1 , E_3 , N_3 , E_{10} , N_{10} , E_{30} , N_{30} for 3 dogs, and N_1 , E_1 , N_3 , E_3 , N_{10} , E_{10} , N_{30} , E_{30} for the other 3 dogs. Recovery of basal cardiovascular parameters was awaited prior to administration of the next dose. Approximate recovery times necessary were: 15 min for 1 μ g kg⁻¹, 20 min for 3 μ g kg⁻¹, 40 min for 10 μ g kg⁻¹ and 60 min for 30 μ g kg⁻¹. Analysis of the effects of the last dose given were followed only for 15 min, sufficient to define maximum effects.

Analysis of results

Cardiovascular parameters were measured just before (pre-dose) and 1, 3, 7 and 15 min after each bolus administration and the percentage changes from corresponding pre-drug values were calculated. Results are expressed as means $\pm$ s.e.mean.

The effects of equal doses of elgodipine and nicardipine were compared at each of the dose levels tested. To identify significant differences between these two drugs, statistical analysis was performed on the individual absolute values using a three-way analysis of variance. In addition, to evaluate the effects of individual treatments, comparisons between values obtained at baseline (pre-dose) and at each subsequent measurement period were performed using a Dunnett test. For all cases the threshold for significance was fixed at $P < 0.05$.

Drugs

Elgodipine (IQB) and nicardipine (Sandoz Pharma) were dissolved in an isotonic solution of glucose (5%). Atropine methyl nitrate (Merck) and ($\pm$)-propranolol hydrochloride (Erypharma) were dissolved in saline (0.9%). Other drugs used were α -chloralose (Prolabo) and sodium thiopentone (Rhone Merieux).

Results

Tables 1 and 2 contain the basal values of cardiovascular parameters in the two experimental groups i.e. under control conditions and following cardiac autonomic blockade, prior to each drug dose. No significant differences were found (ANOVA) between the pre-dose values prior to elgodipine and the pre-dose values prior to nicardipine for each dose level compared (e.g. E_{30} and N_{30}).

In general the group of animals pretreated with propranolol and atropine demonstrated a lower heart rate, higher LVEDP, reduced cardiac contractility, reduced cardiac output, slower AV conduction and higher total peripheral resistance compared with the untreated group of animals.

The vehicle used for administration of the calcium antagonists (5 ml of isotonic glucose, i.v.) produced no significant modification of cardiovascular parameters in these groups of animals.

Table 1 Chloralose-anaesthetized dogs; basal values of cardiovascular parameters in the control group before each bolus dose

Parameters	Units	Elgodipine 1 µg kg ⁻¹	Nicardipine 1 µg kg ⁻¹	Elgodipine 3 µg kg ⁻¹	Nicardipine 3 µg kg ⁻¹	Elgodipine 10 µg kg ⁻¹	Nicardipine 10 µg kg ⁻¹	Elgodipine 30 µg kg ⁻¹	Nicardipine 30 µg kg ⁻¹
Heart rate	beats min ⁻¹	140 ± 6	136 ± 5	138 ± 5	136 ± 5	137 ± 7	136 ± 6	139 ± 7	132 ± 6
Systolic blood pressure	mmHg	126 ± 6	127 ± 6	125 ± 5	125 ± 5	121 ± 5	124 ± 5	122 ± 4	122 ± 5
Diastolic blood pressure	mmHg	89 ± 4	90 ± 5	88 ± 4	87 ± 4	84 ± 3	85 ± 4	82 ± 4	81 ± 3
Mean blood pressure	mmHg	102 ± 5	102 ± 5	101 ± 4	100 ± 4	96 ± 4	98 ± 4	95 ± 4	95 ± 3
Pulmonary arterial pressure	mmHg	32 ± 2	32 ± 2	32 ± 1	32 ± 2	31 ± 1	31 ± 2	30 ± 2	29 ± 1
Left ventricular end diastolic pressure	mmHg	9.5 ± 0.7	9.6 ± 0.5	9.2 ± 0.6	9.2 ± 0.5	8.6 ± 0.6	8.7 ± 0.5	7.9 ± 0.6	7.8 ± 0.5
Left ventricular dP/dt_{max}	mmHg s ⁻¹	2333 ± 245	2354 ± 255	2354 ± 251	2354 ± 273	2312 ± 260	2363 ± 262	2383 ± 244	2408 ± 223
Aortic blood flow	l min ⁻¹	1.72 ± 0.17	1.70 ± 0.17	1.72 ± 0.14	1.73 ± 0.16	1.73 ± 0.12	1.70 ± 0.13	1.68 ± 0.10	1.70 ± 0.11
Coronary blood flow	ml min ⁻¹	29.7 ± 5.8	30.0 ± 5.5	31.3 ± 5.4	32.0 ± 5.8	30.3 ± 5.0	31.7 ± 5.1	31.3 ± 4.9	30.0 ± 4.7
Stroke volume	ml beat ⁻¹	12.5 ± 1.6	12.7 ± 1.5	12.5 ± 1.2	12.8 ± 1.4	12.8 ± 1.0	12.6 ± 1.1	12.2 ± 0.9	12.9 ± 1.0
Total peripheral resistance	mmHg l ⁻¹ min	61 ± 5	63 ± 6	60 ± 4	60 ± 5	57 ± 4	59 ± 4	57 ± 3	56 ± 2
Pulmonary vascular resistance	mmHg l ⁻¹ min	13.7 ± 1.2	13.8 ± 1.3	13.3 ± 1.1	13.3 ± 1.3	12.5 ± 0.6	13.0 ± 0.6	12.3 ± 0.8	11.6 ± 0.8
Coronary vascular resistance	mmHg ml ⁻¹ min	4.07 ± 0.70	3.95 ± 0.64	3.68 ± 0.59	3.62 ± 0.59	3.59 ± 0.54	3.51 ± 0.54	3.40 ± 0.51	3.49 ± 0.44
Mycardial oxygen consumption index	10 ⁻³ ml O ₂ min ⁻¹ g ⁻¹	13.0 ± 0.8	12.7 ± 0.7	12.8 ± 0.8	12.7 ± 0.7	12.4 ± 0.8	12.5 ± 0.8	12.4 ± 0.8	12.1 ± 0.7
PR interval duration	ms	79 ± 3	80 ± 3	80 ± 3	80 ± 3	81 ± 3	79 ± 3	79 ± 3	79 ± 3
Corrected QT interval duration	ms	316 ± 14	312 ± 15	309 ± 13	309 ± 13	310 ± 12	306 ± 12	310 ± 12	302 ± 12

Values are means ± s.e.mean (*n* = 6).**Table 2** Chloralose-anaesthetized dogs; basal values of cardiovascular parameters in the group of animals pretreated with propranolol and atropine before each bolus dose

Parameters	Units	Elgodipine 1 µg kg ⁻¹	Nicardipine 1 µg kg ⁻¹	Elgodipine 3 µg kg ⁻¹	Nicardipine 3 µg kg ⁻¹	Elgodipine 10 µg kg ⁻¹	Nicardipine 10 µg kg ⁻¹	Elgodipine 30 µg kg ⁻¹	Nicardipine 30 µg kg ⁻¹
Heart rate	beats min ⁻¹	127 ± 7	125 ± 7	125 ± 7	125 ± 7	125 ± 7	123 ± 6	122 ± 7	121 ± 6
Systolic blood pressure	mmHg	127 ± 9	128 ± 9	125 ± 9	124 ± 8	122 ± 7	123 ± 6	116 ± 5	119 ± 6
Diastolic blood pressure	mmHg	89 ± 7	90 ± 6	85 ± 6	85 ± 5	81 ± 4	81 ± 4	72 ± 3	76 ± 3
Mean blood pressure	mmHg	102 ± 7	103 ± 7	99 ± 7	98 ± 6	94 ± 5	95 ± 5	86 ± 3	91 ± 4
Pulmonary arterial pressure	mmHg	27 ± 2	27 ± 2	26 ± 2	26 ± 2	26 ± 2	26 ± 2	24 ± 1	25 ± 2
Left ventricular end diastolic pressure	mmHg	11.0 ± 1.0	11.2 ± 0.8	10.6 ± 0.8	11.0 ± 0.8	10.2 ± 0.8	10.1 ± 0.7	9.4 ± 0.7	9.7 ± 0.8
Left ventricular dP/dt_{max}	mmHg s ⁻¹	1833 ± 133	1908 ± 142	1883 ± 151	1867 ± 151	1912 ± 134	1925 ± 109	1863 ± 134	1908 ± 110
Aortic blood flow	l min ⁻¹	1.22 ± 0.10	1.23 ± 0.08	1.25 ± 0.08	1.23 ± 0.08	1.25 ± 0.06	1.30 ± 0.07	1.27 ± 0.07	1.28 ± 0.06
Coronary blood flow	ml min ⁻¹	26.7 ± 4.5	27.3 ± 4.3	28.0 ± 4.6	28.7 ± 4.3	28.0 ± 3.3	30.0 ± 4.3	27.7 ± 2.8	28.3 ± 3.2
Stroke volume	ml beat ⁻¹	9.7 ± 0.9	10.0 ± 0.8	10.1 ± 0.8	10.0 ± 0.8	10.2 ± 0.8	10.8 ± 0.9	10.7 ± 1.2	10.8 ± 1.1
Total peripheral resistance	mmHg l ⁻¹ min	88 ± 14	86 ± 11	81 ± 9	81 ± 9	77 ± 6	75 ± 6	70 ± 5	72 ± 5
Pulmonary vascular resistance	mmHg l ⁻¹ min	14.0 ± 2.6	13.3 ± 2.6	13.0 ± 2.3	13.1 ± 2.3	13.2 ± 1.9	12.6 ± 2.1	11.5 ± 0.9	12.1 ± 1.4
Coronary vascular resistance	mmHg ml ⁻¹ min	4.25 ± 0.69	4.08 ± 0.56	3.89 ± 0.58	3.65 ± 0.40	3.60 ± 0.44	3.42 ± 0.39	3.30 ± 0.36	3.40 ± 0.39
Mycardial oxygen consumption index	10 ⁻³ ml O ₂ min ⁻¹ g ⁻¹	11.3 ± 0.9	11.4 ± 0.9	11.1 ± 0.9	11.0 ± 0.9	10.8 ± 0.7	11.0 ± 0.7	10.3 ± 0.6	10.5 ± 0.6
PR interval duration	ms	92 ± 3	91 ± 3	91 ± 3	90 ± 3	90 ± 3	90 ± 3	89 ± 3	90 ± 3
Corrected QT interval duration	ms	324 ± 9	326 ± 7	325 ± 8	324 ± 7	318 ± 7	320 ± 7	316 ± 6	318 ± 6

Values are means ± s.e.mean (*n* = 6).

Figure 1 Comparison of the haemodynamic profiles of elgodipine (○) and nicardipine (●) in the control group of anaesthetized dogs, i.e. those having functional baroreflexes. Effects of a series of i.v. bolus doses of each compound are shown against coronary blood flow, coronary vascular resistance, diastolic blood pressure, aortic blood flow, total peripheral resistance and mean blood pressure. Points on the graphs represent mean % changes from pre-dose values $\pm$ s.e.mean ($n = 6$), measured 1, 3, 7 and 15 min after dosing. * $P < 0.05$ versus predosing value; † $P < 0.05$ elgodipine versus nicardipine.

Effects of elgodipine and nicardipine in non-pretreated animals

Figures 1 and 2 show a comparison of the effects produced by the different doses of elgodipine and nicardipine on twelve selected parameters in the control group of animals.

The systemic and coronary vasodilator effects of elgodipine and nicardipine were virtually identical. Over the dose range 1–30 $\mu\text{g kg}^{-1}$, i.v., both compounds produced quantitatively-similar, dose-related falls in coronary vascular resistance, total peripheral resistance and diastolic blood pressure accompanied by increases in coronary flow. Nicardipine, as a

consequence of reflex cardiac stimulation, caused a slightly greater rise in cardiac output than elgodipine with correspondingly smaller reductions in systolic (not shown) and mean blood pressures. In general, the vasodilator effects of both compounds were rapid in onset, peaking after 1 min and recovering gradually thereafter with full recovery requiring 10–40 min depending upon the dose. Pulmonary vascular resistance was also reduced to the same extent by both drugs although the magnitude of the fall was smaller than that observed in systemic or coronary vascular beds ($-26 \pm 4\%$ after elgodipine 30 $\mu\text{g kg}^{-1}$, $-24 \pm 5\%$ after nicardipine 30 $\mu\text{g kg}^{-1}$). Pulmonary arterial pressure rose to a greater

Figure 2 Comparison of the haemodynamic profiles of elgodipine (○) and nicardipine (●) in the control group of anaesthetized dogs, i.e. those having functional baroreflexes. Effects of a series of i.v. bolus doses of each compound are shown against heart rate, left ventricular $dP/dt_{\max}$, myocardial oxygen consumption, left ventricular end diastolic pressure, pulmonary arterial pressure and PR interval duration. Points on the graphs represent mean % changes from pre-dose values $\pm$ s.e.mean ($n = 6$), measured 1, 3, 7 and 15 min after dosing. * $P < 0.05$ versus predosing value; † $P < 0.05$ elgodipine versus nicardipine.

extent following nicardipine than following elgodipine (Figure 2).

The vasodepressor effects of nicardipine were accompanied by dose-related increases in cardiac contractility ($dP/dt_{\max} + 27 \pm 7\%$ at $30 \mu\text{g kg}^{-1}$) and heart rate ($+16 \pm 5\%$ at $30 \mu\text{g kg}^{-1}$) which were statistically significant at all doses studied. Elgodipine, despite causing similar or greater falls in blood pressure, did not significantly increase heart rate except after $3 \mu\text{g kg}^{-1}$ ($+8 \pm 4\%$). Nicardipine-induced changes in heart rate were greater than those associated with elgodipine at all doses (difference reached statistical significance after 1, 10 and $30 \mu\text{g kg}^{-1}$). This contrast between the two compounds is particularly marked at $30 \mu\text{g kg}^{-1}$ (Figure

2). While nicardipine produced a substantial reflex tachycardia which was well sustained throughout the period during which blood pressure was lowered, heart rate was unchanged following elgodipine. Elgodipine produced significant dose-related increases in $dP/dt_{\max}$ which were less marked than those observed after nicardipine (significantly different at the two highest doses). As illustrated by the decrease in PR interval duration, both compounds accelerated AV nodal conduction at 3 and $10 \mu\text{g kg}^{-1}$ but not at the highest dose tested where elgodipine, in fact, showed a tendency to increase PR interval duration. Nicardipine caused dose-related increases in MVO_2 ($+23 \pm 9\%$ after $30 \mu\text{g kg}^{-1}$) whereas elgodipine did not significantly affect this parameter. This

Figure 3 Comparison of the haemodynamic profiles of elgodipine (O) and nicardipine (●) in anaesthetized dogs pretreated with propranolol and atropine to block cardiac autonomic tone. Effects of a series of i.v. bolus doses of each compound are shown on selected parameters, coronary vascular resistance, myocardial oxygen consumption, heart rate, left ventricular dP/dt_{max} , PR interval duration and QTc interval duration. Points on the graphs represent mean % changes from pre-dose values $\pm$ s.e.mean ($n = 6$), measured 1, 3, 7 and 15 min after dosing. * $P < 0.05$ versus predosing value; † $P < 0.05$ elgodipine versus nicardipine.

difference between the two compounds was statistically significant at 10 and 30 $\mu\text{g kg}^{-1}$. Neither drug affected LVEDP at low doses although elgodipine significantly increased this parameter at the highest dose.

Effects of elgodipine and nicardipine in animals pretreated with atropine and propranolol

Drug effects on selected parameters following elimination of cardiac reflex tone using the combination of propranolol and atropine are shown in Figure 3. Cardiac parameters are displayed preferentially since analysis of the direct cardiac

effects of the two products was the objective of this part of the study.

After cardiac autonomic blockade the coronary (Figure 3) and systemic vasodilator properties of elgodipine and nicardipine were quantitatively similar but generally less prominent than observed in the absence of atropine and propranolol. Maximum reduction in total peripheral resistance following the highest doses of elgodipine and nicardipine were $-26 \pm 7\%$ and $-29 \pm 6\%$ in animals pretreated with propranolol and atropine, and $-43 \pm 4\%$ and $-44 \pm 4\%$ in non-pretreated animals, respectively. However, marked differences between the compounds were apparent on heart rate (Figure

3). Elgodipine $1\text{--}30\text{ }\mu\text{g kg}^{-1}$ produced dose-related bradycardia, significant at all doses ($-21 \pm 3\%$ at $30\text{ }\mu\text{g kg}^{-1}$) whereas nicardipine caused mild reductions in heart rate only at the two highest doses ($-8 \pm 2\%$ at $30\text{ }\mu\text{g kg}^{-1}$). Comparison of the dose-response curves indicates that elgodipine was approximately ten times more potent than nicardipine in reducing heart rate. At 10 and $30\text{ }\mu\text{g kg}^{-1}$, the bradycardia induced by elgodipine was slowly developing and prolonged compared to that induced by nicardipine. Both compounds caused dose-related inhibition of cardiac contractility and slowing of AV nodal conduction starting at $3\text{ }\mu\text{g kg}^{-1}$ (Figure 3). For both parameters the effects of elgodipine were more pronounced than those of nicardipine, this difference being significant at the higher doses. Unlike nicardipine, elgodipine ($30\text{ }\mu\text{g kg}^{-1}$) resulted in a small but statistically significant abbreviation of the QTc interval ($-7 \pm 3\%$) of the ECG. In the presence of atropine and propranolol, both elgodipine and nicardipine dose-dependently decreased MVO_2 , but the effects of elgodipine were longer lasting than those of nicardipine.

It is interesting to note that the difference in heart rate response between the two compounds observed when reflexes were functional was already maximal 1 min after dosing, whereas, following atropine and propranolol the greater inhibitory effect of elgodipine manifests itself progressively, becoming maximal 7 min after dosing. At 1 min the compounds showed similar decelerator properties.

Discussion

As vasodilators in our model, elgodipine and nicardipine appeared extremely similar and well-matched. Both produced dose-related peripheral and coronary vasodilatation over the range studied ($1\text{--}30\text{ }\mu\text{g kg}^{-1}$, i.v.) with a potency which was essentially equivalent. In addition, their vasodilator responses had similar kinetic characteristics and durations. A more detailed analysis of the data illustrates that both calcium antagonists showed a very slight selectivity for the coronary bed (e.g. elgodipine $3\text{ }\mu\text{g kg}^{-1}$ produced $37 \pm 3\%$ reduction in coronary vascular resistance and $30 \pm 5\%$ reduction in total peripheral resistance). Since the coronary vascular bed autoregulates in response to changes in myocardial oxygen demand part of the coronary vasodilatation observed after nicardipine may have been due to the increase in MVO_2 . This phenomenon is unlikely to contribute to elgodipine-induced coronary vasodilatation since elgodipine, unlike nicardipine, did not significantly elevate MVO_2 under control conditions. Despite similar pulmonary vasodilator effects, nicardipine increased pulmonary arterial pressure to a greater extent than elgodipine. This effect may be related to the reflex increase in cardiac output which tended to be more pronounced with nicardipine. Neither compound increased pulmonary artery pressure in dogs pretreated with atropine and propranolol (data not shown).

The equivalence of nicardipine and elgodipine as vasodilators in the control group contrasted with the dissimilarity of their cardiac profiles. Systemic vasodilatation and hypotension caused by nicardipine were accompanied at all doses by cardiac stimulation of reflex origin (tachycardia and inotropy). In these and other respects the profile of nicardipine was very similar to that previously reported for nifedipine in the same model (Humphries & O'Connor, 1988). Maintenance of anaesthesia with chloralose favours the manifestation of reflex cardiac effects since chloralose impairs baroreflex function to a lesser extent than other types of anaesthetic (Chenoweth & Van Dyke, 1969). Elgodipine also produced marked falls in diastolic blood pressure ($-36 \pm 4\%$ after $30\text{ }\mu\text{g kg}^{-1}$, i.v.) but in contrast to nicardipine, these were associated with little or no reflex tachycardia. However, elgodipine did elicit significant reflex positive inotropic effects at all doses although these were smaller than produced by nicardipine. The studies performed in the presence of

atropine and propranolol reveal that elgodipine has an important intrinsic inhibitory action on sinus rate. In this respect it was approximately ten times more potent than nicardipine despite having equivalent vasodilator potency. Suppression of reflex tachycardia by elgodipine is therefore largely due to this direct decelerator action of long duration which was present throughout the vasodilator dose-range.

Analysis of the temporal changes in heart rate and blood pressure suggests that, at least following $30\text{ }\mu\text{g kg}^{-1}$, i.v., elgodipine, an additional property (over and above the direct decelerator action) may contribute to suppression of reflex tachycardia in the control group of animals. In this group of animals with functional reflexes, 1 min after dosing heart rate was unchanged following elgodipine administration whereas nicardipine-induced reflex tachycardia was maximal. However, at this time point in animals pretreated with atropine and propranolol, the direct decelerator effect of elgodipine was sub-maximal and not different from that of nicardipine. This suggests that elgodipine also possesses an anti-accelerator property of neurogenic origin which comes into operation rapidly to reduce reflex elevations of heart rate. One possible explanation would be an inhibitory effect of elgodipine on baroreceptor function. Changes in baroreceptor sensitivity have been reported following administration of other calcium antagonists (Heesch *et al.*, 1983; Warltier *et al.*, 1984).

The cardiovascular profile of elgodipine and, in particular, its ability to cause systemic and coronary vasodilatation without significant reflex tachycardia, distinguishes it from most other dihydropyridines which would tend to demonstrate a nicardipine-like profile in this model. However, FPL 62129 (Humphries & O'Connor, 1988) and MDL 72567 (Difrancesso *et al.*, 1986) are dihydropyridines which have also been reported to lower blood pressure acutely without reflex tachycardia in a fashion similar to elgodipine. In terms of overall profile, elgodipine appears to be positioned midway between, at one extreme, the vascular-selective dihydropyridines and, at the other, calcium antagonists of the verapamil and diltiazem types which show much more prominent direct cardiac effects, particularly on sinus and AV nodes (Taira, 1987). Presumably the mechanism responsible for the direct decelerator effect of elgodipine involves block of L-type calcium channels which play an important role in impulse generation and conduction in nodal tissues. In addition to blocking L-type calcium channels, elgodipine has been shown to possess antagonistic activity at T-type calcium channels in rat portal vein (J. Mironneau, personal communication). A similar T-type calcium channel exists in cardiac tissue where it is thought to have a role in pacemaker function (Hagiwara *et al.*, 1988). Therefore the possible involvement of T-channel block in the potent direct decelerator action of elgodipine cannot be excluded.

Haemodynamic studies with elgodipine in the anaesthetized pig (Sassen *et al.*, 1990) and in the conscious pig following myocardial infarction (van Woerkens *et al.*, 1991) have shown that elgodipine-induced vasodilatation is not associated with significant depression of cardiac contractility, leading to the suggestion that elgodipine would be suitable for use in congestive heart failure. However, our data indicate that elgodipine demonstrates only a moderate degree of vascular selectivity (i.e. vasodilator potency compared with depression of cardiac contractility) and is less vascular-selective than nicardipine. In our study the two compounds were equipotent as vasodilators while elgodipine produced greater inhibition of dP/dt_{max} than nicardipine when cardiac autonomic tone was eliminated. Similarly, reflex increases in dP/dt_{max} were smaller following elgodipine than with nicardipine. Clearly, there are many differences between the present study and those performed in the pig by other investigators (e.g. species, methodology, anaesthesia), however our comparison of nicardipine and elgodipine in the same animals remains a key element for interpretation of the data. Our study suggests that elgodipine does not possess marked vascular selectivity

and, under conditions when reflex cardiac activation is impaired (as commonly occurs in heart failure), manifests a negative inotropic effect at doses of $3 \mu\text{g kg}^{-1}$, i.v. and greater. Therefore, it may not offer advantages over nicardipine in the treatment of heart failure.

When viewed in the context of angina the haemodynamic profile of elgodipine appears more attractive. Reflex tachycardia is an undesirable consequence of acute vasodilatation which may worsen cardiac ischaemia, either as a result of increased myocardial oxygen demand, or by reducing diastolic filling time thus impairing coronary perfusion (Boudoulas *et al.*, 1979). Unlike nicardipine which, when reflexes were functional, produced dose-related increases in MVO_2 , elgodipine did not change this parameter significantly. Hence in our model, elgodipine shows potent coronary vasodilatation unaccompanied by increases in MVO_2 , suggesting that it will have a favourable effect on myocardial oxygen supply/demand balance, a profile appropriate for the treatment of angina. To illustrate the possible clinical significance of this difference in profile between elgodipine and nicardipine, the latter drug has been reported to show pro-ischaemic properties (associated with tachycardia) in coronary artery disease patients (Lambert *et al.*, 1985; Gheorghiade *et al.*, 1989). However, whether elgodipine offers clinically-significant advantages over other dihydropyridines remains to be established. Reflex tachycardia to nifedipine is largely an acute phenomenon tending to diminish on chronic treatment and

may be countered by co-administration of a β -adrenoceptor blocker, a regime which is acceptable in angina patients.

The effects of elgodipine on ECG are of interest in the light of a report (Bellissant *et al.*, 1991) that the compound, rather unexpectedly given the absence of changes in arterial pressure and heart rate, accelerated AV conduction and ventricular repolarization in human volunteers. In the anaesthetized dog, elgodipine produced changes in PR interval which were clearly the composite of reflex acceleration of AV nodal conduction and, at high doses, the direct conduction slowing property of the compound. In this respect the profile of elgodipine was as predicted, qualitatively similar to nicardipine and very like that of FPL 62129 (Humphries & O'Connor, 1988). However unlike nicardipine, elgodipine, at the highest dose tested, produced a small but statistically significant decrease in QTc interval, indicative of accelerated ventricular repolarization. Since this occurred in the presence of atropine and propranolol it represents a direct cardiac effect of the compound. The mechanism and the significance of this observation remain to be established.

In summary, elgodipine has systemic and coronary vasodilator properties similar to those of nicardipine but more important direct inhibitory cardiac effects, particularly with respect to the sinus node. Unlike nicardipine its hypotensive effects in chloralose-anaesthetized dog are not accompanied by reflex tachycardia or increases in MVO_2 .

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(Received August 17, 1993)

Accepted September 6, 1993