Nitrendipine and the humoral control of sodium homeostasis

D. R. FORSYTH* & C. J. C. ROBERTS

The University Department of Medicine, Bristol Royal Infirmary, Bristol

- 1 Nine healthy volunteers received 10 mg nitrendipine or placebo orally in random order.
- 2 In the subsequent 5 h urinary sodium excretion was 20% higher after nitrendipine, without any significant difference between the volume of urine excreted after nitrendipine or placebo. Mean blood pressure fell by 5 mm Hg ($P < 0.001$), and mean heart rate increased by 5 beats min^{-1} ($P < 0.01$) after nitrendipine but did not change after placebo.
- 3 These changes were accompanied by a significant elevation in plasma renin activity ($P < 0.001$). A fall in plasma aldosterone following placebo appeared to be attenuated by nitrendipine. Plasma noradrenaline increased to a peak 3 h after nitrendipine administration ($P < 0.05$) but did not change following placebo. A fall in the excretion of 6-keto $\text{PGF}_{1\alpha}$ following placebo was attenuated by nitrendipine. The total excretion of 6-keto $\text{PGF}_{1\alpha}$ after nitrendipine was significantly greater ($P < 0.05$) than after placebo but no difference in the total excretion of PGE_2 was detected. Nitrendipine did not affect urinary kallikrein excretion.
- 4 The natriuretic action of nitrendipine is not mediated by the kallikrein-kinin system, but may be related to changes in renal prostaglandins.

Keywords nitrendipine natriuresis prostaglandins

Introduction

Nitrendipine is a new dihydropyridine calcium antagonist effective in the treatment of hypertension (Pedrinelli *et al.*, 1986; Thananopavarn *et al.*, 1984). Of importance in selecting an antihypertensive agent is its effect on renal physiology (Hollenberg, 1984). Calcium antagonists unlike other vasodilators, such as hydralazine, diazoxide, prazosin, methyl dopa and minoxidil are not associated with sodium retention secondary to reflex stimulation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (Koch-Weser, 1974), but have been shown to cause a natriuresis following first administration (Edgar *et al.*, 1984; Ene *et al.*, 1985; Van Schaik *et al.*, 1984). Ankle oedema may occur, especially with nifedipine, this is not however due to fluid retention as there is no concomitant weight increase (Pedersen *et*

al., 1980), but is thought to be due to a redistribution of body fluids as a result of vasodilation (Ene *et al.*, 1985). The natriuretic property of calcium antagonists may be a factor in their therapeutic action in hypertension.

The mechanism of the natriuretic action of nitrendipine (Ene *et al.*, 1985) and other calcium antagonists (Edgar *et al.*, 1984; Ene *et al.*, 1985; Van Schaik *et al.*, 1984) might depend upon their influence on the renin-angiotensin-aldosterone and kallikrein-kinin systems and intrarenal prostaglandins, all of which play a part in intrarenal sodium homeostasis (Ylitalo, 1984). The aim of this study was to ascertain the immediate effect of oral nitrendipine on plasma catecholamines, plasma renin activity, plasma aldosterone, urinary prostaglandins and urinary kallikreins and to relate these to the drug's

Present address and address for correspondence: Dr D. R. Forsyth, Department of Medicine for the Elderly, Royal Devon and Exeter Hospital (Heavitree), Gladstone Road, Exeter EX1 2ED.

effects on blood pressure, heart rate and electrolyte excretion.

Methods

Nine healthy volunteers (six female) of mean age 27 years (range 22–39 years) were studied. None was taking any drug and the females were not on the oral contraceptive. The female subjects were all studied mid-menstrual cycle. Full blood count, urea and electrolytes and liver function tests were performed at entry and 1 week after completion of the study. The study design was approved by the Bristol and Weston Health Authority Ethics Committee. All volunteers gave written informed consent. Subjects were instructed verbally and by provision of a diet sheet to avoid extremes of sodium and potassium intake and encouraged to eat a consistent diet for 1 week before commencing any measurements. Urinary sodium excretion was measured in a 24 h urine collection obtained 48 h before commencing the study. All subjects refrained from alcohol, tobacco, caffeine, vigorous exercise and sexual intercourse for at least 48 h prior to any measurements.

The study design was single-blind to the volunteers and consisted of 2 non-consecutive days of measurements at least 1 week apart. On both days the subjects attended the laboratory after an 8 h overnight fast. After voiding urine (which was discarded) and the insertion of a heparinised line into a forearm vein, they took 300 ml of water orally. Subjects then remained semi-recumbent (sitting in a chair reading) standing only to void urine. At the end of the first hour basal venous blood samples were taken for urea, sodium, potassium, catecholamines, plasma aldosterone and plasma renin activity (PRA). At this time urine was also collected, volume measured and aliquots frozen at -20°C for later measurement of urea, sodium, potassium, prostaglandin E_2 (PGE_2) and 6-keto prostaglandin $\text{F}_{1\alpha}$ (6-keto $\text{PGF}_{1\alpha}$) and kallikrein. Subjects then took either matching placebo or 10 mg nitrendipine orally according to a random allocation. A further 300 ml oral water was then taken each hour thereafter to ensure adequate urine flow. Venous blood and urine samples were collected hourly for a further 5 h. Blood pressure and heart rate were measured hourly throughout, with the subjects semi-recumbent. Blood pressures were recorded by a single observer using a standard mercury sphygmomanometer [Accoson] and phase V diastolic, heart rate was measured over 1 min at the radial pulse.

Sample collection and analysis

Full blood counts, liver function tests, plasma and urinary urea, sodium and potassium were analysed using automated analysers. Blood samples for catecholamines, aldosterone and PRA were kept on ice after collection and plasma separated in a refrigerated centrifuge. Plasma catecholamines were analysed by radioenzymatic technique modified from the method by Peuler & Johnson (1977). Samples for PRA were collected into tubes containing EDTA and 100 μl of distilled water. Plasma renin activity was analysed by an indirect measurement assaying the generation of angiotensin I from renin present in the sample using a radioimmunoassay with rabbit antibody (Haber *et al.*, 1969). Samples for aldosterone were collected in tubes containing lithium heparin. Plasma aldosterone was analysed by radioimmunoassay technique using a commercial kit without extraction (CIS (UK) Ltd, London).

Urinary kallikreins were assayed by the functional amidase substrate method to measure both active and total kallikrein and by radioimmunoassay to measure total kallikrein (O'Hare *et al.*, 1986). Urinary PGE_2 was measured by radioimmunoassay and 6-keto $\text{PGF}_{1\alpha}$ by negative ion chemical ionisation gas chromatography mass spectrometry (Watson *et al.*, 1984).

Calculations and statistical analysis

Mean blood pressure was calculated as: diastolic + $\frac{1}{3}$ (systolic – diastolic) blood pressure in mm Hg.

Multifactor analysis of variance was used to measure the significance of any changes during drug administration compared with placebo. A probability of less than 0.05 was taken as significant. All results are expressed as mean $\pm$ s.e. mean.

Results

All subjects completed the study protocol and there was no adverse drug reaction. No abnormality was found in their full blood counts, liver function tests or plasma urea, sodium and potassium before or after the study. Twenty-four hour urinary sodium excretion measured 2 days before each study day was similar prior to both placebo ($87.3 \pm 9.3 \text{ mmol l}^{-1}$) and nitrendipine ($95.7 \pm 14.0 \text{ mmol l}^{-1}$).

Effects on urinary sodium excretion

Baseline urinary sodium excretion was the same ($10.6 \pm 2.0 \text{ mmol h}^{-1}$) on the placebo (range 4–21 mmol h^{-1}) and nitrendipine (range 3–23 mmol h^{-1}) days. Mean urinary sodium excretion increased during the first 3 h after administration of nitrendipine by 19% at maximum to $12.6 \pm 1.3 \text{ mmol h}^{-1}$ (range 6–21 mmol h^{-1} ; $P = 0.18$) whereas that after placebo fell by 18% to $8.7 \pm 1.3 \text{ mmol h}^{-1}$ (range 4–13 mmol h^{-1}) (Figure 1). Total urinary sodium excretion in the 5 h after nitrendipine administration was 20% higher ($56.9 \pm 4.6 \text{ mmol}$; range 34–72 mmol) than after placebo ($47.3 \pm 4.1 \text{ mmol}$; range 29–70 mmol ; $P = 0.05$).

Effects on urine volume

There was a rise in mean urine volume in the first and second hours after both placebo and nitrendipine. Mean urine volume increased by 88% after nitrendipine from $259 \pm 44 \text{ ml h}^{-1}$ to $487 \pm 39 \text{ ml h}^{-1}$ ($P < 0.001$) and by 53% after placebo from $279 \pm 85 \text{ ml h}^{-1}$ to $426 \pm 43 \text{ ml h}^{-1}$ ($P = 0.07$) (Figure 2). Total mean urine volumes over the 5 h of the study were $1694 \pm 41 \text{ ml}$ after nitrendipine and $1636 \pm 86 \text{ ml}$ after placebo (NS).

Effects on urinary potassium excretion

There was a steady fall in mean urinary potassium excretion after both nitrendipine and placebo ($P = 0.04$ for both) but no difference between the two in this respect (Table 1). The total amount of potassium excreted in the 5 h after nitrendipine was $22.4 \pm 2.7 \text{ mmol}$ and $22.2 \pm 3.7 \text{ mmol}$ after placebo.

Figure 1 Mean $\pm$ s.e. mean urinary sodium excretion in nine healthy subjects during the 5 h following the administration of 10 mg of nitrendipine (○) orally compared with that after placebo (●).

Figure 2 Mean $\pm$ s.e. mean urine volume in nine healthy subjects during the 5 h following the administration of 10 mg of nitrendipine (○) orally compared with that after placebo (●).

Effects on blood pressure and heart rate

Mean blood pressure was similar at baseline on the two occasions. After nitrendipine it gradually fell to its lowest level at 4 h, from $83 \pm 2 \text{ mm Hg}$ to $78 \pm 2 \text{ mm Hg}$ ($P = 0.0002$), whereas no change was observed with placebo. Heart rate increased from $69 \pm 3 \text{ beats min}^{-1}$ to $74 \pm 4 \text{ beats min}^{-1}$ in the first 3 h after nitrendipine ($P = 0.006$) but changed insignificantly after placebo from $66 \pm 3 \text{ beats min}^{-1}$.

Effects on plasma renin activity

Mean plasma renin activity (PRA) was similar at baseline on the two occasions. A rise in PRA was recorded after placebo but this was significantly greater after nitrendipine ($P = 0.0004$). The difference between the effects of the two was most evident at 1 and 2 h after administration (Figure 3).

Effects on plasma aldosterone

Mean baseline levels of plasma aldosterone were higher on the day of placebo administration ($95.1 \pm 10.6 \text{ pg ml}^{-1}$) compared with the day of nitrendipine administration ($78.3 \pm 6.0 \text{ pg ml}^{-1}$). There was a steady fall in plasma aldosterone levels after placebo to $64.0 \pm 6.1 \text{ pg ml}^{-1}$. There was an initial fall in plasma aldosterone levels in the first hour after nitrendipine to $65.0 \pm 5.4 \text{ pg ml}^{-1}$ and a rise towards baseline values there-

Table 1 Mean urinary excretion of potassium, plasma potassium; aldosterone and adrenaline in nine healthy subjects during the 5 h following the administration of 10 mg of nitrendipine (N) orally compared with that after placebo (P) (s.e. mean in parentheses)

Time (h)	Urinary potassium (mmol)		Plasma potassium (mmol l ⁻¹)		Plasma aldosterone (pg ml ⁻¹)		Plasma adrenaline (nmol l ⁻¹)	
	P	N	P	N	P	N	P	N
0	6.2 (0.9)	5.3 (1.3)	4.01 (0.08)	4.08 (0.13)	95.1 (10.6)	78.3 (6.0)	0.18 (0.06)	0.08 (0.02)
1	5.9 (0.8)	5.7 (1.4)	4.00 (0.07)	4.06 (0.09)	72.6 (9.5)	65.0 (5.4)	0.32 (0.19)	0.15 (0.04)
2	5.1 (0.8)	4.3 (0.4)	3.90 (0.05)	3.86 (0.04)	67.0 (7.9)	77.1 (8.5)	0.13 (0.03)	0.16 (0.04)
3	4.2 (1.1)	4.3 (0.6)	3.90 (0.07)	3.93 (0.06)	69.3 (7.2)	77.7 (9.1)	0.11 (0.02)	0.25 (0.11)
4	4.0 (0.6)	4.3 (0.6)	3.79 (0.05)	3.86 (0.08)	67.4 (8.2)	72.7 (10.4)	0.27 (0.12)	0.19 (0.04)
5	3.0 (0.7)	3.8 (0.5)	3.76 (0.06)	3.77 (0.04)	64.0 (6.1)	72.9 (9.3)	0.20 (0.03)	0.18 (0.04)

Figure 3 Mean $\pm$ s.e. mean plasma renin activity in nine healthy subjects during the 5 h following the administration of 10 mg of nitrendipine (○) orally compared with that after placebo (●).

after (Table 1). These differences were not statistically significant.

Effects on plasma adrenaline and noradrenaline

Mean plasma adrenaline levels varied widely at each time interval on the day of placebo administration. There was a gradual increase in plasma adrenaline levels after the administration of nitrendipine from a baseline value of 0.08 ± 0.02 nmol l⁻¹ to 0.25 ± 0.11 nmol l⁻¹ in the third hour, decreasing to 0.18 ± 0.04 nmol l⁻¹ by the end of the study (Table 1).

Mean plasma noradrenaline levels were unchanged after placebo (Figure 4) but were consistently higher than at baseline throughout the study after nitrendipine ($P = 0.026$). The peak increase in plasma noradrenaline level was in the third hour after administration of nitrendipine (2.43 ± 0.3 nmol l⁻¹ compared with 1.59 ± 0.18 nmol l⁻¹).

Effects on urinary prostaglandin excretion

Excretion of 6-keto PGF_{1 α} fell consistently (Figure 5) after both placebo and nitrendipine ($P = 0.0001$ for both). The fall was greatest after placebo, so that the total amount of 6-keto PGF_{1 α} excreted in the 5 h after nitrendipine

Figure 4 Mean $\pm$ s.e. mean plasma noradrenaline in nine healthy subjects during the 5 h following the administration of 10 mg of nitrendipine (○) orally compared with that after placebo (●).

Figure 5 Mean $\pm$ s.e. mean urinary excretion of 6-keto $\text{PGF}_{1\alpha}$ in nine healthy subjects during the 5 h following the administration of 10 mg of nitrendipine (○) orally compared with that after placebo (●).

($74.1 \pm 5.4 \text{ ng ml}^{-1} \text{ h}^{-1}$) was significantly greater than after placebo ($61.7 \pm 2.8 \text{ ng ml}^{-1} \text{ h}^{-1}$; $P = 0.03$). PGE_2 excretion fell after both placebo and nitrendipine except in the fourth hour after nitrendipine when it increased by 27% (Figure 6), from $83.6 \pm 26.3 \text{ pg ml}^{-1} \text{ h}^{-1}$ to $106.0 \pm 45.2 \text{ pg ml}^{-1} \text{ h}^{-1}$. The total amount of PGE_2 excreted in the 5 h after administration of nitrendipine was $263.0 \pm 53.9 \text{ pg ml}^{-1}$ compared with $223.9 \pm 62.0 \text{ pg ml}^{-1}$ after placebo (NS).

Figure 6 Mean $\pm$ s.e. mean urinary excretion of PGE_2 in nine healthy subjects during the 5 h following the administration of 10 mg of nitrendipine (○) orally compared with that after placebo (●).

Effects on urinary kallikrein excretion

There was no statistically significant difference in the excretion rates of total urinary kallikrein or active urinary kallikrein during the course of the study. The mean rates of excretion of total and active urinary kallikrein in the 5 h after administration of nitrendipine were $7265 \pm 318 \text{ ng ml}^{-1} \text{ min}^{-1}$ and $57.2 \pm 2.3 \text{ mu ml}^{-1} \text{ min}^{-1}$ compared with $7907 \pm 277 \text{ ng ml}^{-1} \text{ min}^{-1}$ and $56.3 \pm 2.2 \text{ mu ml}^{-1} \text{ min}^{-1}$ after placebo (NS respectively).

Effects on plasma sodium and potassium

Plasma potassium concentration fell significantly ($P < 0.001$) after both placebo and nitrendipine administration (Table 1) and by a similar amount. Plasma sodium concentration did not alter after either placebo or nitrendipine.

Discussion

This study has demonstrated an increase in sodium excretion in the 5 h after nitrendipine administration, consistent with previous reports of an acute natriuretic action of this drug (Ene *et al.*, 1985; Wallia *et al.*, 1985). The water loads given in this study are likely to have obscured the acute diuretic action of nitrendipine seen by

Ene *et al.* (1985). Although mean urine volume increased by 88% in the first hour after nitrendipine, there was a subsequent phase of antidiuresis. This corresponded with the onset of the drug's haemodynamic effect, as evidenced by the fall in systemic blood pressure and rise in heart rate. The overall renal response to nitrendipine is likely to be the resultant of a direct renal tubular action modified by the decrease in blood pressure and its effect on renal perfusion and by indirect effects of the drug on the kidney and dependent on experimental conditions (Hollenberg, 1984; Wallia *et al.*, 1985; Zanchetti & Leonetti, 1985).

The small increase in heart rate seen in this study is a consistent finding with nitrendipine (Thananopavarn *et al.*, 1984; Ventura *et al.*, 1983) and other dihydropyridine calcium antagonists (Corea *et al.*, 1979; Van Shaik *et al.*, 1984). This is due to a baroreceptor mediated reflex increase in sympathetic activity as evidenced by the increase in plasma noradrenaline levels seen in this study and others (Corea *et al.*, 1979; Muiesan *et al.*, 1982; Ventura *et al.*, 1983). The lack of an effect of nitrendipine on plasma adrenaline levels is consistent with previous studies with dihydropyridine calcium antagonists which have shown either a small increase (Kiowski *et al.*, 1983; Pedrinelli *et al.*, 1986) or no effect (Kiowski *et al.*, 1983; Muiesan *et al.*, 1982; Thananopavarn *et al.*, 1984) and with the phenyl-alkylamine, verapamil, which has no effect (Muiesan *et al.*, 1982; Van Shaik *et al.*, 1984). Stimulation of renal noradrenergic α_1 -adrenoceptors increases renal tubular sodium and water reabsorption (Osborn *et al.*, 1983) and will tend to oppose any natriuretic action of calcium antagonists (Johns, 1985).

The rise in plasma renin activity (PRA) after nitrendipine was small but statistically significant, and was not accompanied by any significant increase in plasma aldosterone concentrations. Reflex stimulation of the renin-angiotensin-aldosterone system might be expected with nitrendipine as a consequence of its vasodilatory and natriuretic properties (Koch-Weser, 1974). However a number of studies have failed to show any consistent effect of nitrendipine (Fouad & Pedrinelli, 1982; Thananopavarn *et al.*, 1984) or other calcium antagonists (Aoki *et al.*, 1978; Katzman *et al.*, 1986; Muiesan *et al.*, 1982; Tsunoda *et al.*, 1986) on PRA or plasma aldosterone levels.

The fall in plasma potassium seen in this study might be expected to stimulate renin secretion and inhibit the production of aldosterone (Williams & Dluhy, 1983). It has been suggested

that renin and aldosterone production are calcium dependent events (Olgaard *et al.*, 1978; Watkins *et al.*, 1976) and so the chemical heterogeneity of the calcium antagonists might explain their differing effects on the renin-angiotensin-aldosterone system (Aoki *et al.*, 1978; Fouad & Pedrinelli, 1982; Katzman *et al.*, 1986; Muiesan *et al.*, 1982; Thananopavarn *et al.*, 1984; Tsunoda *et al.*, 1986; Ventura *et al.*, 1983). Finally, the angiotensin-II mediated stimulation of aldosterone production may be inhibited by the calcium antagonists (Hiramatsu *et al.*, 1982; Millar *et al.*, 1981).

The increase in urinary excretion of PGE_2 in the fourth hour after nitrendipine corresponded to the drug's peak haemodynamic effect. An increase in urinary excretion of PGE_2 has also been seen with diltiazem (Nagao *et al.*, 1985) and nifedipine (Tsunoda *et al.*, 1986). It is likely that this is due to an increased renal synthesis rather than an increased wash-out of PGE_2 (Zawada, 1984) as it was not seen with placebo. Although urinary excretion of 6-keto $\text{PGF}_{1\alpha}$ did not rise, nitrendipine appeared to attenuate the fall seen after placebo so that the total urinary excretion of 6-keto $\text{PGF}_{1\alpha}$ was greater than after placebo. Thus, any increase in PGE_2 synthesis may not be related to a direct renal effect of nitrendipine but be secondary to stimulation of the sympathetic system or renin and aldosterone secretion (Salvetti & Pedrinelli, 1982). Activation of the kallikrein-kinin-prostaglandin system by nifedipine has been shown to be independent of any change in plasma aldosterone (Tsunoda *et al.*, 1986). If nitrendipine's natriuretic action were mediated through its effects on renal prostaglandins, a selectivity for PGE_2 would favour a tubular site of action (Forsyth & Roberts, 1988; Wallia *et al.*, 1985). However, PGE_2 may influence tubular sodium reabsorption indirectly by causing a redistribution of renal cortical and medullary blood flow (Ylitalo, 1984).

The results of this study would suggest that the natriuretic effect of nitrendipine is not mediated via the kallikrein-kinin system. This is in keeping with a previous study using nifedipine (Madeddu *et al.*, 1987). In the absence of any effect of nitrendipine on the kallikrein-kinin system it is unlikely that any increase in PGE_2 synthesis is mediated via the kallikrein-kinin system (Ylitalo, 1984).

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