The effect of 8 weeks treatment with the calcium antagonist felodipine on blood pressure, heart rate, working capacity, plasma renin activity, plasma angiotensin II, urinary catecholamines and aldosterone in patients with essential hypertension

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- 1 The effect of 8 weeks treatment with the calcium antagonist felodipine—a new long-acting dihydropyridine derivative—in a dose of 10 mg twice daily was studied in 10 male patients with essential hypertension, WHO grade I–II, aged 25–62 years.
- 2 Diastolic blood pressure was reduced in supine and upright position. Systolic blood pressure was reduced only in the upright position. Heart rate was unchanged in the supine and decreased in the upright position.
- 3 During dynamic exercise blood pressure was reduced. The maximal working capacity decreased, whereas the maximal heart rate attained was unchanged.
- 4 Twenty-four hour urinary noradrenaline excretion, plasma renin activity and 24 h urinary aldosterone excretion were increased. Plasma angiotensin II and 24 h urinary adrenaline excretion were unchanged.
- 5 In conclusion, felodipine is an effective long-acting blood pressure lowering drug with minor side effects. After 8 weeks on felodipine treatment heart rate was not increased, although the activity of the sympathetic nervous system and the renin-aldosterone system seemed enhanced.

Keywords felodipine blood pressure maximal work test catecholamines renin–aldosterone

Introduction

An increase in peripheral vascular resistance is the common haemodynamic disturbance in established essential hypertension. The final determinant of vascular tone in resistance vessels is the intracellular free calcium ion concentration (Filo *et al.*, 1965).

Calcium antagonists have been shown to block calcium influx and to bind to membrane proteins associated with excitable calcium channels in the cell membrane (Fleckenstein, 1983).

Felodipine is a new long acting dihydropyridine calcium antagonist. Treatment with felodipine

for 3–7 days in patients with essential hypertension lowered blood pressure with a concomitant increase in heart rate (Andersson *et al.*, 1984, Leonetti *et al.*, 1985). Long term monotherapy with felodipine has not previously been studied.

We have investigated the effect of felodipine treatment for a longer period (8 weeks) in patients with essential hypertension on supine and upright blood pressure, heart rate and indices of sympathetic activity and the activity in the renin-aldosterone system. The study was performed during standardized conditions. In addition we

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studied the effect of felodipine on blood pressure, heart rate and maximal working capacity on an outpatient basis using bicycle ergometry.

Methods

Patients

Ten male patients (Table 1) with previously untreated essential hypertension, WHO grade I–II, were studied. The diagnosis was based on clinical examination, blood and urinary analyses including plasma renin activity, urinary catecholamines and aldosterone, intravenous rapid sequence pyelography and in three cases renal angiography. All patients showed normal ECG with the exception of patient no 4 who had an anterolateral hemiblock. None presented proteinuria. I.v. rapid sequence pyelography was normal in nine patients, in patient no 10 a renal cyst with a diameter of 4 cm was found. Following puncture of the cyst, renal angiography was normal. With the exception of moderate gonarthrosis in patient no 4 no other concomitant diseases were disclosed. No medication except felodipine was given during the study.

The study protocol was approved by the Committee of Ethics, Medical Faculty, University of Lund. Written consent was obtained from all patients.

Basal conditions

Studies were performed with the patients hospitalized in a metabolic ward for 6 days, before treatment and after an 8 week treatment period. In hospital they were maintained on a diet containing 150 mmol Na⁺ and 75 mmol K⁺ daily. Identical investigations were performed during the two hospitalization periods.

Blood pressure (mercury sphygmomanometer) and pulse rate were recorded by a trained nurse after the patient had been supine for at least 15 min and after 2 min standing on day 4 and 5 of hospitalization at 08.00 h, 12.00 h, 16.00 h and 20.00 h. Diastolic blood pressure was taken at Korotkoff phase V.

Twenty-four hour urinary collections were performed on days 4 and 5.

For the analyses of plasma renin activity and plasma angiotensin II blood samples were drawn at 10.00 h after 10 min in the sitting position in nine patients.

Maximal work test

A maximal work test was performed on an outpatient basis before and after 8 weeks on felodi-

pine treatment (see below) in nine patients. Patient no 4 was excluded due to gonarthrosis. An electronically braked bicycle ergometer (Ergomed 740, Siemens-Elema) was used and ECG was continuously recorded. After resting in a sitting position for 10 min, the patients started with an initial work load of 70 W. This was maintained for 4 min and then increased in steps of 10 W min⁻¹ until exhaustion. Blood pressure was measured by one and the same investigator (U.L.H.) with a mercury sphygmomanometer before exercise and then every second minute. Diastolic values are taken at Korotkoff phase IV. Heart rate was measured from ECG.

Medication

Medication started with felodipine plain tablets in a dose of 5 mg twice daily taken at 08.00 h and 20.00 h. The patients were seen after 1 week and the dose was then increased to 10 mg twice daily which was maintained over the second hospitalization period.

Analytical methods

Urinary catecholamines were measured by a fluorometric method (von Euler & Lishajko, 1961) and urinary aldosterone by radioimmunoassay (Ogihara *et al.*, 1977).

Plasma renin activity was determined as the amount of angiotensin I generated following incubation for 1 h at pH 6.0 (Haber *et al.*, 1969; Cohen *et al.*, 1971). Plasma angiotensin II was measured by radioimmunoassay after extraction (Kappelgaard *et al.*, 1976).

All samples collected from each patient, under the respective conditions, before and during felodipine were analyzed in one and the same assay run, and the intraassay variability was: 6% for noradrenaline (measured at a range of 14–167 nmol l⁻¹); 15% for adrenaline (range 2.2–21.0 nmol l⁻¹); 5% for aldosterone (range 1.9–44.5 nmol l⁻¹); 8% for renin (range 0.9–2.3 µg l⁻¹ h⁻¹); and 8% for angiotensin II (range 2.9–57.4 pmol l⁻¹).

Statistical evaluation

Statistical analysis was performed by nonparametric methods. Statistical significance of difference in blood pressure and heart rate (mean of the 8 measurements performed day 4 and 5) during basal conditions was assessed by the Wilcoxon matched-pairs signed-ranks test (Figure 1), whereas the Friedman two-way analysis of variance by ranks was used when the

Table 1 Ambulatory clinical and laboratory findings in the 10 patients studied

Patient	Age (years)	Body weight/height (kg/cm)	Supine BP (mm Hg)	Cardiac size (ml m ⁻²)	Serum potassium (mmol l ⁻¹)	Serum creatinine (μmol l ⁻¹)	Upright PRA (μg l ⁻¹ h ⁻¹)	U-aldosterone (nmol 24 h ⁻¹)	U-noradrenaline (nmol 24 h ⁻¹)	U-adrenaline (nmol 24 h ⁻¹)
1	25	97.9/181	185/120	390	4.4	85	1.0	39.2	131	25
2	26	77.5/167	160/105	460	3.9	83	0.9	8.2	93	20
3	42	82.8/176	160/105	440	4.1	101	1.8	17.9	120	22
4	54	100.2/176	140/100	650	4.1	102	0.6	16.1	125	11
5	49	84.0/174	160/110	420	4.2	81	1.3	11.8	137	21
6	62	72.7/185	180/100	290	4.1	105	0.3	20.1	64	14
7	55	73.9/177	170/110	400	4.2	86	0.6	7.1	92	36
8	57	78.9/177	170/115	390	4.1	83	0.7	18.5	134	18
9	32	92.2/180	155/110	400	3.9	106	1.3	8.1	114	19
10	54	90.0/176	160/105	370	3.9	81	0.6	7.6	78	28
Normal range					3.5-5.0	60-115	0.2-2.0	5.0-16.0	60-300	0-60

difference in blood pressure and heart rate (mean of the two measurements performed day 4 and 5) before and on felodipine at 08.00 h, 12.00 h, 16.00 h and 20.00 h was compared.

Statistical significance of difference in plasma renin activity, plasma angiotensin II concentration, urinary catecholamines and aldosterone excretion (mean of two 24-h urinary collections) was assessed by the Wilcoxon matched-pairs signed-ranks test (Figures 2 and 3).

Statistical analysis of differences in blood pressure and heart rate during exercise before and on felodipine treatment was performed from 0 to 10 min (all nine patients included) by the Wilcoxon matched-pairs signed-ranks test. A Bonferroni correction (Miller, 1966) was used to allow for the six comparisons which were made on each variable (Figure 5). The Friedman two-way analysis of variance by ranks were applied for the comparison of the increase in blood pressure and heart rate from 0–10 min before and on felodipine treatment. The Wilcoxon matched-pairs signed-ranks test was used to compare maximal work load and maximal heart rate attained during exercise before and on felodipine treatment.

The level of significance was taken as $P < 0.05$. All data in text and figures are presented as mean $\pm$ 1 s.d.

Results

Basal blood pressure and heart rate

Felodipine treatment lowered diastolic blood pressure in the supine and upright position. Systolic blood pressure was reduced in the upright but not significantly in the supine position. During felodipine treatment heart rate was unchanged in the supine position, but decreased in the upright position (Figure 1). The effect of felodipine on blood pressure and heart rate was maintained from 08.00 h–20.00 h except for the reduction in upright diastolic blood pressure, which was less pronounced immediately before felodipine intake ($P < 0.05$).

Renin-angiotensin II-aldosterone-catecholamines

Plasma renin activity increased after felodipine treatment. Plasma angiotensin II concentration was not significantly changed, but was higher in seven of nine patients after felodipine (Figure 2). Urinary aldosterone as well as noradrenaline excretion increased after felodipine treatment, whereas urinary excretion of adrenaline did not change (Figure 3).

Figure 1 Mean blood pressure and heart rate 08.00–20.00 h in supine and upright position before (○, □) and during (●, ■) felodipine treatment for 8 weeks (mean $\pm$ 1 s.d.). * $P < 0.05$, ** $P < 0.01$.

Maximal work test

Maximal working capacity was significantly reduced during felodipine (Figure 4), but the maximal heart rate attained at termination of exercise did not differ (179 ± 11 vs 177 ± 8 beats min⁻¹).

Felodipine significantly lowered systolic and diastolic blood pressure during exercise (Figure 5). The exercise-induced increase in systolic blood pressure and heart rate was similar before and during felodipine treatment.

Side effects

Felodipine was well tolerated. Tachycardia was reported by some patients during the first week of medication, but regular measurements were not performed. After 8 weeks of treatment three patients spontaneously reported transient mild palpitations 1–2 h after tablet intake. Two patients noticed transient nocturnal ankle oedema. Body weight was unchanged following felodipine treatment (before 83.3 ± 10.5 , after 82.9 ± 10.9 kg).

Discussion

In an earlier study short term monotherapy with felodipine in patients with essential hypertension

Figure 2 Sitting plasma renin activity and angiotensin II concentration before (□) and during (▨) felodipine treatment for 8 weeks (mean $\pm$ 1 s.d.). * $P < 0.05$.

Figure 3 Urinary aldosterone, noradrenaline and adrenaline excretion — mean of two 24 h urinary collections — before (□) and during (▨) felodipine treatment for 8 weeks (mean $\pm$ 1 s.d.). * $P < 0.05$, ** $P < 0.01$.

was shown to reduce blood pressure concomitant with an increase in heart rate (Anderson *et al.*, 1984). In the present study a persistent reduction of blood pressure without a consistent change in heart rate was found after 8 weeks of felodipine treatment. The present findings on blood pressure and heart rate are similar to those reported by Gould *et al.* (1982), Muesan *et al.* (1982), Kiowski *et al.* (1983) and McLeay *et al.* (1983) concerning the effect of another dihydropyridine

Figure 4 Maximal working capacity before and during felodipine treatment for 8 weeks (mean $\pm$ 1 s.d.). * $P < 0.05$.

They found reduced blood pressure with unaltered supine heart rate after 6–16 weeks treatment with nifedipine in patients with essential hypertension. On the other hand, Lederballe Pedersen *et al.* (1979) reported increased heart rate after 6 weeks of nifedipine treatment in hypertensive patients.

The lack of an increase in heart rate, in spite of a distinct reduction of blood pressure, in the present study may partly be due to a resetting of the arterial baroreceptors as shown in spon-

Figure 5 Blood pressure and heart rate in connection with a maximal work test before and during felodipine treatment for 8 weeks (mean $\pm$ 1 s.d.). Statistical evaluation has been performed 0–10 min ($n = 9$) and a Bonferroni correction has been used. * $P < 0.05$.

taneously hypertensive rats after 2 weeks treatment with felodipine (Nordlander, 1985) and during long term treatment with nifedipine in patients with essential hypertension (McLeay *et al.*, 1983).

Although urinary noradrenaline excretion was increased after 8 weeks of felodipine treatment, the heart rate was unchanged. These findings concur with earlier findings by Muiesan *et al.* (1982) who reported unchanged heart rate and increased plasma noradrenaline concentration after 2 months nifedipine treatment in patients with essential hypertension. On the other hand they are at variance with those of Lederballe Pedersen *et al.* (1979) and Kiowski *et al.* (1983) who reported unchanged plasma and/or urinary noradrenaline levels after 6 weeks on nifedipine treatment in patients with essential hypertension. The reason for this discrepancy is not obvious. Urinary noradrenaline excretion mainly reflects general sympathetic activity, but may partly be of renal origin (Willis *et al.*, 1980). The increase in noradrenaline excretion with unchanged heart rate may indicate unchanged activity in cardiac sympathetic nerves in spite of an increase in general sympathetic activity. A differential sympathetic outflow has previously been reported after carotid nerve stimulation in

man (Wallin *et al.*, 1975). Alternatively, the β -adrenoceptor mediated chronotropic effect of sympathetic stimulation may be attenuated by felodipine. This would be in analogy with the attenuation of α -adrenoceptor-mediated vasoconstriction shown with nifedipine in normal subjects (Beretta-Picoli *et al.*, 1982). Other plausible explanations for the increase in urinary noradrenaline are increased renal clearance or decreased whole body clearance of noradrenaline, as shown after β -adrenoceptor blockade (Cryer *et al.*, 1980). The effect of calcium antagonists on these variables have to our knowledge not been reported.

Plasma renin activity was found to be increased with a concomitant increase in urinary aldosterone excretion after 8 weeks on felodipine treatment. This increase in plasma renin activity may be secondary to an increase in sympathetic activity (Höckfelt *et al.*, 1968). A direct effect of felodipine on the juxtaglomerular cell with a decrease in intracellular free calcium concentration may also contribute to renin release (Kawamura & Inagami, 1983). Furthermore the inhibitory effect of angiotensin II on renin release was reported to be attenuated by the calcium antagonist D-600 (Naftilan & Oparil, 1982). Finally, an inhibitory action on the calmodulin-calcium

complex in the juxtaglomerular cell could also induce renin release (Boström *et al.*, 1981, Kawamura & Inagami, 1983). Somewhat at variance with the present finding Lederballe-Pedersen *et al.* (1979), Muiesan *et al.* (1982), Kiowski *et al.* (1983) and McLeay *et al.* (1983), found unaltered plasma renin activity and plasma aldosterone concentration after long-term treatment with nifedipine in hypertensive patients. However, with the exception of Muiesan *et al.* (1982) these investigators also reported unchanged plasma and/or urinary noradrenaline levels.

In our study felodipine reduced systolic and diastolic pressure during exercise. These findings are in accordance with those of Lund-Johansen & Omvik (1983), who after long-term treatment with nifedipine found a significant blood pressure reduction during graded exercise in hypertensive patients.

The maximal heart rate attained during exercise was of the same magnitude before and during felodipine treatment. This is similar to

the findings of Raffestin *et al.* (1985), who studied the haemodynamic effect of a single sublingual dose of nifedipine in normal subjects during exercise on bicycle ergometer. During physical exercise blood is redistributed from the vascular beds of resting skeletal muscles, kidneys, splanchnic area and skin, to working skeletal muscles, due to increased sympathetic activity during exercise (Rowell, 1974). The vasodilatory action of felodipine with a decrease in α -adrenoceptor-mediated vasoconstriction may lead to a hyperperfusion of resting skeletal muscles, kidneys, splanchnic area and skin during exercise. This could explain the decrease in maximal working capacity found in the present study. The unaltered maximal work load after acute nifedipine administration to normotensive subjects in the study by Raffestin *et al.* (1985) may be due to a less pronounced vasodilatory action of calcium antagonists in normotensive as compared to hypertensive subjects (Hulthén *et al.*, 1982; Robinson *et al.*, 1982; Hulthén *et al.*, 1983; Yokoyama & Kaburagi, 1983).

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