Short-term effects of felodipine, a new dihydropyridine, in hypertension

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1 Felodipine, a dihydropyridine, is a new vasodilating calcium antagonist which lowers blood pressure (BP) by selective action on vascular smooth muscle, especially in the resistance vessels.

2 The effects on BP, heart rate (HR) and tolerance of different single oral doses of felodipine were studied in two series of hypertensive patients. When felodipine was given as single drug to 14 previously untreated hypertensives in a single-blind manner, BP was rapidly reduced by about 15% while HR increased by 25%. Felodipine given in a double-blind manner to eight patients on chronic β -adrenoceptor blockade reduced BP by some 15–20% compared to placebo, while HR did not change.

3 There was a significant correlation between the pre-treatment mean arterial BP (MAP) and the maximal relative change in MAP, i.e. the higher the initial BP the greater the reduction after felodipine. A significant correlation was also found between the plasma concentration of felodipine and the relative change in MAP.

4 Felodipine was generally well tolerated. When given alone felodipine caused the side effects expected from a pure vasodilator, i.e. headache, flushing and palpitations. When given together with a β -adrenoceptor blocker, the side effects were much less apparent.

Keywords dihydropyridine felodipine vasodilatation anti-hypertensive

Introduction

In patients with established hypertension the peripheral arterial resistance is increased and, in many cases, the addition of a vasodilating agent is needed to reduce the blood pressure (BP) satisfactorily (Andersson *et al.*, 1978). Available vasodilating drugs often have disadvantages regarding potency or side effects, and therefore the development of new vasodilators is justified.

Felodipine (H 154/82) is a new dihydropyridine (4-(2, 3,-dichlorophenyl)-1, 4-dihydro-2, 6-dimethyl - 3 - ethoxycarbonyl - 5 - methoxycarbonylpyridine), which in therapeutic concentrations selectively reduces smooth muscle tone, parti-

cularly in the resistance vessels. In *in-vitro* experiments, concentrations 100 times higher than those needed to decrease smooth muscle tone are needed to produce a corresponding negative inotropic effect on papillary muscle (Ljung, 1980). The effect on the myocardium may be due to so-called calcium blockade (Fleckenstein, 1977). However, the relaxation of arteriolar smooth muscle is probably mediated only partly by blockade of Ca^{2+} influx and it has been suggested that it is more likely a result of intracellular action (Boström *et al.*, 1981).

In animal studies felodipine has been shown to

reduce peripheral resistance and BP at plasma concentrations (Cp) from about 20 nmol/l (Ek *et al.*, 1980). A close relationship between Cp of felodipine and haemodynamic effects was seen. In healthy male volunteers an increased cardiac output due to increased heart rate (HR) and stroke volume was found at Cp from 15 nmol/l. In addition, the diastolic (DBP) and mean BP (MAP) and thus peripheral resistance were reduced (Johnsson *et al.*, 1983). The HR was increased in healthy men during an observation period of 7 h after an oral administration. When the compound was given after metoprolol, no significant change in HR was observed.

To evaluate the effects of felodipine on BP, HR and tolerance in hypertensive patients, two series of patients were investigated. The studies were designed to investigate the acute effects of different doses of felodipine in single therapy, as well as in combination with β -adrenoceptor blockade.

Methods

All patients gave their informed consent to the trial. The study was approved by the Ethical Committees of the Medical Faculties of the Universities involved.

Single-blind study

Fourteen men, aged 22–62 (mean 48 ± 11) years with previously untreated, moderately severe, primary hypertension were selected for the trial. Only subjects with an ambulatory DBP (Phase V) of 106–125 mm Hg in the supine position were eligible. This BP was the mean of four readings (two measurements with an interval of 15 min at two out-patient visits).

The patients were hospitalised for 5 days. On the day of admittance (day 0) routine examinations were performed and the patients became acquainted with the ward and the BP measurements. On the next day (day 1) placebo (capsules identical in appearance to felodipine) was given at 08.00 h and 25 mg felodipine at 13.00 h. On the following days (days 2–4) felodipine was administered orally in doses of 25, 50 and 100 mg. Felodipine was given as gelatine capsules, containing 25 mg of the compound, which had been dissolved and sprayed on granules. The dose titration was done individually, taking the BP reduction and side effects into account. The dose was not further increased if the MAP 1–1.5 h (mean) after felodipine was reduced by 20% or more compared to pre-drug readings.

Supine BP and HR were recorded 60, 30 and 0 min before and hourly after, administration of placebo or felodipine until 21.00 h (15.00 h on the last day). The means of the BP and HR recorded before tablet administration were taken as control values for each day. For the last day (when 100 mg metoprolol was administered at 07.00 h) the HR at 08.00 h was used as the control value. The BP and HR were measured with a semi-automatic device, the DinaMap BP recorder (Silas *et al.*, 1980; Ramsey, 1979) after 5 min rest in the supine position and after 1 min in the standing position. All recorded values were the mean of two measurements. In the hospital ward the patients were not confined to bed and had the ordinary hospital meals.

An electrocardiogram (ECG) was taken before felodipine was given and 2 h after administration of the individual maximal dose. Routine blood chemistry and urine tests were performed before and at the end of the study. Body weight was recorded before and during treatment. Blood for the determination of the plasma concentration (Cp) of felodipine was drawn at defined intervals. The compound was analysed by gas chromatography and electron capture detection (Ahnoff, to be published).

Double-blind study

Eight patients, six women and two men, aged 52–65 years (mean 60 ± 4), with essential hypertension, WHO stages I or II, were included in the trial. Their blood pressures were not satisfactorily controlled with chronic, optimal β -adrenoceptor blockade as the sole antihypertensive therapy. Only subjects with supine DBP ≥ 100 mm Hg as the mean value of readings after 1 and 2 weeks' addition of placebo were included in the study.

The patients were randomly allocated to double-blind treatment with felodipine or placebo. Between the two regimens there was a wash-out period of 1 week's duration when placebo was given. The β -adrenoceptor blocker dosage was unchanged throughout the study. A single dose of felodipine (mean 16 ± 7 , range 6.25–25 mg) as a tablet formulation (phase II tablet) or corresponding placebo was given in the morning and the patients were kept under observation for 2 h at the clinic.

Exclusion criteria

Both in the single-blind and in the double-blind study patients with systolic BP (SBP) over 230 mm Hg, myocardial infarction, angina pectoris, cardiac failure, diabetes mellitus or laboratory

signs of renal or liver disease were excluded, nor were subjects in whom β -adrenoceptor antagonists were contraindicated eligible.

Statistical analyses

Statistical analyses of changes in BP and HR were made by means of the Wilcoxon matched-pairs signed rank test. The statistical analyses of the laboratory tests were made using Student's *t*-test for paired variables. The correlation between the percentage change in MAP and the control MAP was measured by Spearman's rank order correlation. The relation between the relative change in MAP and the logarithms of the felodipine C_p values was studied on the basis of analyses of covariance. The regression and correlation coefficients between MAP and the transformed C_p values were estimated for each patient. The hypothesis of no interaction, i.e. equal regression coefficients for each patient was tested. In case of no interaction the average inter-patient correlation and regression coefficients were estimated from analyses of covariance and their significance was tested. Statistical significance was defined as $P < 0.05$. In tables and text means $\pm$ s.d. are given.

Results

Single-blind study

The mean SBP during the ambulatory, pre-hospital period, were 175 ± 18 and 170 ± 19 mm Hg in the supine and standing positions, respectively. The corresponding DBP were 111 ± 5 and 112 ± 7 mm Hg.

After the administration of placebo on the day after admittance the BP and HR were stable. Four hours after a single dose of 25 mg felodipine the supine BP ($143 \pm 14/84 \pm 9$ mm Hg) was lower ($P < 0.01$) than control BP ($163 \pm 18/102 \pm 9$ mm Hg) and the HR (79 ± 13 beats/min) was increased ($P < 0.01$) compared to control HR (63 ± 8 beats/min). Thus, the SBP and DBP were decreased by 12 and 18%, respectively, and the HR increased 25% (Figure 1). The intake of felodipine caused a consistent, marked and statistically significant decrease in BP and increase in HR after every administration. However, HR did not increase significantly on the last day when the patients had been pre-treated with metoprolol. On that day, 2 h after felodipine, the supine HR was 67 ± 12 beats/min compared to 66 ± 9 beats/min at the control measurement (NS), while the supine BP ($118 \pm 12/72 \pm 11$ mm Hg) was lower ($P < 0.01$) than the control value ($136 \pm 10/85 \pm 7$ mm Hg) (Figure 2). Owing to a pro-

nounced hypotensive effect, some patients did not receive the highest dose of felodipine. Therefore, the average doses of felodipine during the study were 25 and 45 mg once daily on days 1 and 2, respectively, 75 mg twice daily on day 3, and 75 mg once daily on day 4.

The effects were usually apparent after 1 h and maximal after 2–3 h and lasted for 5–7 h.

There was a significant correlation ($r = -0.76$, $P < 0.05$) between control MAP (supine) and the maximal relative change (%) in MAP in the eight patients that received a single dose of 100 mg felodipine (Figure 3).

The maximal C_p of felodipine varied between individuals, with up to a six-fold difference after identical doses. Maximal C_p after the various doses was usually seen 3 h after drug administration. The average correlation between C_p of felodipine and the relative change in supine MAP was significant ($r = -0.46$, $P < 0.001$), (Figure 4).

The only changes in laboratory variables were seen in serum creatinine (94 ± 14 ; 89 ± 14 mmol/l) and cholesterol (5.9 ± 0.3 ; 5.4 ± 0.4 mmol/l), which both decreased slightly but significantly ($P < 0.05$). The patients' mean body weight (82.9 ± 12 ; 83.0 ± 12 kg) did not change during the trial.

The number of patients who reported side effects is given in Table I. Headache was the most frequent side effect and occurred in 10 out of the 14 patients. It was usually mild to moderate. Flush, palpitations and dizziness were also fairly frequent. Flush and palpitations appeared to be dose-dependent. The side effects were less apparent on the last day when the patients were pre-treated with metoprolol. One patient developed transient ST-segment depression on the highest dose level. He had no other signs or symptoms of cardiac involvement.

Double-blind study

Immediately before administration of the first dose of felodipine or placebo, i.e. at the end of the run-in period the blood pressures were $203 \pm 25/112 \pm 6$ and $196 \pm 21/113 \pm 6$ mm Hg in the supine and standing positions, respectively. The corresponding values at the end of the wash-out period were $196 \pm 32/105 \pm 13$ and $187 \pm 31/107 \pm 12$ mm Hg respectively. When comparing these values no significant difference was found. The study could thus be evaluated as an intra-patient comparison of the results for felodipine and placebo.

The decrease in BP after felodipine (compared to pre-drug values) was significantly more pronounced than after placebo at all readings (30, 60 and 120 min after drug) both in the supine and in the standing positions. The change in HR

Figure 1 Systolic and diastolic blood pressure (BP) and heart rate (HR) in the supine (.....) and standing (—) positions after placebo and an oral dose of 25 mg felodipine. Mean values of 14 patients. * indicates values significantly ($P < 0.05$) different from control (C) values.

Figure 2 Systolic and diastolic blood pressure (BP) and heart rate (HR) in the supine (.....) and standing (—) positions before and after a mean oral dose of 75 mg felodipine given 1 h after an oral dose of 100 mg metoprolol. Mean values of 14 patients. * indicates values significantly ($P < 0.05$) different from control (C) values.

Figure 3 Maximal relative change in supine mean arterial pressure (MAP %) after 100 mg oral felodipine in relation to pre-drug blood pressure (control MAP mm Hg).

Figure 4 Individual regression lines and average correlation coefficient (r) for the correlation between relative change in supine mean arterial pressure (MAP %) and log plasma concentration (C_p) of felodipine. The regression lines have been extended to the lowest and the highest C_p found in the 14 patients.

Table 1 Number of hypertensive patients who spontaneously reported side effects during treatment with felodipine. Total number of patients = 14. Single-blind study.

	Headache	Flush	Palpitations	Dizziness
Felodipine 25 mg	4	1	0	1
Felodipine 75 mg	4	5	7	3
Felodipine 75 mg and metoprolol 100 mg	2	1	1	3

did not differ after felodipine compared to placebo. After 2 h supine BP was lowered by 30/19 mm Hg (17/19%) after felodipine compared to placebo. The corresponding difference in standing blood pressure was 34/21 mm Hg (20/21%) (Table 2).

Felodipine was well tolerated and only a few mild to moderate side effects were reported. In three patients flush was observed after felodipine. Two of these patients also reported mild to moderate headache.

Discussion

Single oral doses of felodipine were administered as monotherapy, and in combination with β -adrenoceptor blockade to patients with essential hypertension in order to evaluate effects on BP and HR and tolerability.

Both when administered as monotherapy and in combination with β -adrenoceptor blockade, felodipine had a clear BP-lowering effect. However, when administered alone, felodipine triggered a reflex tachycardia which was also noticed by the patients. When given in addition to a β -adrenoceptor blocker, this increase in HR was not seen. Also, palpitations as well as other

side effects (i.e. headache and flushing) were less apparent. The side effects with acute doses of felodipine are those to be expected after potent vasodilators (Koch-Weser, 1974; Olivari *et al.*, 1979). It is reasonable to believe that such adverse reactions will be reduced during chronic therapy due to adoptive mechanisms such as e.g. resetting of the baroreceptors (Hallback-Nordlander & Thalen, 1983; Kiowski *et al.*, 1983).

Administration of felodipine in addition to a β -adrenoceptor blocker resulted in a marked and rapid reduction in BP when compared to placebo in a double-blind study. In single doses from 6.25 to 25 mg there was no increase in HR and tolerability was good. From a theoretical point of view, the combination of felodipine with a β -adrenoceptor blocker has several advantages. BP reduction is achieved by influencing the main pathophysiological feature in essential hypertension, i.e. the increased systemic vascular resistance, while reflex tachycardia is counteracted by the β -adrenoceptor blocker.

The largest relative BP reductions were seen in the patients with the highest initial BP levels. A similar relationship has previously been described and discussed for nifedipine (Lederballe Pedersen *et al.*, 1980). This relationship could be due to several mechanisms, e.g. a consequence of more

Table 2 Systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR) 0–120 min after a single oral dose of felodipine (tablet). Means $\pm$ s.d. from eight hypertensive patients on chronic treatment with a β -adrenoceptor blocker. Double-blind study.

Time (min)	Felodipine				Placebo			
	0	30	60	120	0	30	60	120
<i>Supine</i>								
SBP	199 $\pm$ 26	175 $\pm$ 20*	154 $\pm$ 16*	146 $\pm$ 19*	198 $\pm$ 35	193 $\pm$ 26	176 $\pm$ 16	176 $\pm$ 18
DBP	108 $\pm$ 5	94 $\pm$ 9*	88 $\pm$ 6*	82 $\pm$ 11*	108 $\pm$ 15	106 $\pm$ 11	103 $\pm$ 10	101 $\pm$ 11
HR	62 $\pm$ 6	59 $\pm$ 4	56 $\pm$ 4	54 $\pm$ 4	63 $\pm$ 9	59 $\pm$ 7	54 $\pm$ 5	51 $\pm$ 6
<i>Standing</i>								
SBP	194 $\pm$ 21	163 $\pm$ 20*	146 $\pm$ 16*	133 $\pm$ 15*	188 $\pm$ 34	182 $\pm$ 29	166 $\pm$ 19	167 $\pm$ 20
DBP	110 $\pm$ 5	94 $\pm$ 11*	86 $\pm$ 5*	80 $\pm$ 13*	109 $\pm$ 14	104 $\pm$ 12	103 $\pm$ 13	101 $\pm$ 12
HR	64 $\pm$ 7	60 $\pm$ 7	56 $\pm$ 5	55 $\pm$ 5	67 $\pm$ 11	59 $\pm$ 7	55 $\pm$ 5	53 $\pm$ 7

* denotes significant difference ($P < 0.05$) between change in blood pressure (BP 0–30, 0–60 and 0–120 min) after felodipine and placebo, respectively.

advanced morphological changes in the resistance vessels in patients with the highest BP levels, or an increased sensitivity to calcium antagonism in the vascular smooth muscle cells in these patients.

After acute administration of felodipine there was a correlation between the reduction in BP and Cp. However, such a relationship may not

necessarily exist during steady-state conditions after chronic dosing.

In conclusion, single doses of felodipine were shown to have a pronounced BP-lowering effect and were well tolerated in combination with a β -adrenoceptor blocker. Further studies of felodipine in hypertensive patients are well justified.

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