Felodipine, Blood Pressure, and Cardiovascular Reflexes in Hypertensive Humans

STEPHEN A. SMITH, PETER J. E. MACE, AND WILLIAM A. LITTLER

SUMMARY The influence of acute and chronic treatment with felodipine on ambulatory intra-arterial blood pressure, certain cardiac reflexes, and plasma renin activity was studied in nine patients with essential hypertension. Acute oral administration of the drug caused a significant reduction in blood pressure associated with an increase in heart rate mediated by the sinoaortic baroreceptor-heart rate reflex. After 1 week of treatment reflex resetting had occurred, returning heart rate to normal despite continuing blood pressure reduction. This effect was maintained throughout 6 weeks of treatment. Withdrawal of treatment was followed by return of the blood pressure to control levels associated with significant bradycardia caused by reflex reactivation at its reset level. No change was observed in response to tilting or Valsalva’s maneuver or in plasma renin activity. Ambulatory intra-arterial data suggested that the clinically useful antihypertensive action of felodipine persists for 9 hours. (Hypertension 8: 1172-1178, 1986)

KEY WORDS • felodipine • sinoaortic baroreceptor reflex • calcium antagonist • hypertension • vasodilator

The antihypertensive action of many vasodilating drugs is antagonized by an increase in sympathetic nervous system activity, which increases heart rate and cardiac output and stimulates the renin-angiotensin system. We have shown that chronic treatment with the calcium antagonist and vasodilator nifedipine1 and with the related drug nicardipine2 can reset the sinoaortic baroreceptor heart rate (SAB-HR) reflex and increase its sensitivity, allowing sustained blood pressure reduction without persistent tachycardia.

Felodipine is a new dihydropyridine calcium channel entry blocker that is similar to nifedipine. It reduces blood pressure principally by its action on vascular smooth muscle3 with minimal effects on myocardial contractility and conduction.4,5 Acute administration of this drug reduces peripheral vascular resistance and blood pressure with an increase in heart rate and cardiac output.6

The aims of this study were 1) to examine the acute and chronic effects of felodipine on ambulatory intra-arterial blood pressure, SAB-HR reflex sensitivity, and set point; the responses to tilt and Valsalva’s maneuver; and the renin-angiotensin system in hypertensive humans, and 2) to investigate the time course of SAB-HR reflex resetting.

Patients and Methods

Nine patients (5 men, 4 women) with an age range of 35 to 59 years (mean, 46.3 years) and with an average outpatient casual blood pressure of (mean ± SD) 186 ± 21/110 ± 8 mm Hg were enrolled and completed the acute part of the study. One patient was withdrawn after 1 week of treatment because of failure to cannulate the brachial artery. Two other patients were withdrawn during the chronic treatment period because they did not wish to continue with the study. There were no withdrawals related to adverse effects of felodipine treatment. Six patients completed the study.

All the patients had essential hypertension with diastolic blood pressure (DBP) greater than 100 mm Hg on three separate occasions, measured with a Hawksley random zero sphygmomanometer (Gelman Hawksley Ltd., Lancing, UK) after 5 minutes of supine rest. The mean known duration of hypertension was 47 months (range, 9 months to 15 years). No patient had evidence of target organ damage, defined as evidence of ischemic heart disease, cerebrovascular disease, renal impairment, or malignant hypertension, and none had received antihypertensive treatment for at least 1 month before enrollment.
Study Design

The study was approved by the hospital ethical committee. Figure 1 outlines the study protocol. After informed consent had been obtained, the patients were admitted to our cardiovascular investigation ward and started on felodipine-matched placebo before control evaluation of SAB-HR reflex sensitivity, responses to tilt and Valsalva's maneuver, and plasma renin activity (PRA). These investigations were repeated the next day 2 hours after subjects received a 10-mg tablet of felodipine. Patients were then discharged on a regimen of orally administered felodipine at a dose of 5 mg (6 subjects) or 7.5 mg (3 subjects) twice daily, and further assessments of cardiovascular reflexes and PRA were made at 1 week and 6 weeks. They were then transferred to a felodipine-matched placebo, and the assessments were made again 24 hours later (i.e., 6 weeks + 1 day).

Casual blood pressure was measured on each study day, 2 hours after the morning tablet of felodipine or placebo. The means of three readings were taken after 5 minutes of supine rest and after 2 minutes of standing. Using a Hawksley random zero indirect sphygmomanometer. Heart rate, weight, and ankle circumference were also recorded.

Ambulatory intra-arterial blood pressure recordings were made before the acute study while patients were receiving placebo and at the end of the chronic study.

Cardiovascular Reflexes

On each study day the first dose of felodipine or matched placebo was given at 0800. Cardiovascular reflexes were assessed between 1000 and 1200 in a quiet laboratory with a constant ambient air temperature of 28°C. Intra-arterial blood pressure, respiratory movements, and the electrocardiogram were recorded simultaneously on a multichannel physiological recorder (Grass Medical Instruments, Quincy, MA, USA). Measurements subsequently were taken from the paper record using a high resolution (<0.1 mm) graphics tablet (Terminal Display Systems, Blackburn, UK). Unless otherwise stated, all recordings were made with the patient resting supine on a mechanical tilting table.

The SAB-HR reflex sensitivity was measured using a modification of the method of Gribbin et al.7 Bolus doses of phenylephrine were injected to give a transient increase in systolic blood pressure (SBP) of approximately 25 mm Hg. Each SBP value throughout the rise was plotted against its corresponding pulse interval. The slope of the regression line of pulse interval on SBP is a measure of the sensitivity of the reflex. The reflex set point is determined from values of SBP and corresponding pulse intervals measured at least 30 minutes after insertion of the cannulas, prior to the reflex assessments and following 20 minutes of supine rest.

Following supine control measurements, subjects were rapidly tilted to 65 degrees (head up) and maintained in that position for 15 minutes. Standardized Valsalva's maneuvers were performed as previously described.8 The patients were asked to blow through a mouthpiece into an aneroid manometer, maintaining a reading of 30 mm Hg for 15 seconds. Mean blood pressure and pulse interval were measured during each of the usual four phases. We have subdivided Phase II into IIA (the lowest pressure in the first part of Phase II) and IIB (the peak of the rise occurring later in Phase II). The Valsalva ratio, defined as the longest pulse interval in Phase 4 divided by the shortest pulse interval during the strain, was also measured. Results given are the arithmetic mean of data extracted from at least three separate Valsalva's maneuvers.

Intra-arterial Blood Pressure Measurement

All patients underwent ambulatory intra-arterial blood pressure monitoring using the Oxford technique.9 Briefly, arterial pressure was measured directly through a 1-mm internal diameter Teflon cannula inserted with the patient under local anesthesia into the left brachial artery and connected to a miniature pressure transducer and perfusion device (Romulus Technology, London, UK). The transducer signal was recorded on a portable analog tape recorder (Oxford Medical Systems, Abingdon, UK). A Nova 3 (Data General, Southboro, MA, USA) computer was then used to digitize the signal and produce hourly average SBP and DBP and heart rate. Average blood pressures during sleep, waking activity, and the whole study period were calculated. Blood pressure variability is represented by the standard deviation of the frequency histogram.10

All recordings were made in an open hospital ward from 1200 until 0800 the following day; mealtimes, visiting hours, and drug administration times were standardized. Duration of action of felodipine was determined by analysis of hourly SBP and DBP in the 12 hours following the 2000 dose. During this time, patients rested quietly or slept, no meals were taken, and no other investigations were performed.

![Protocol](http://hyper.ahajournals.org/graphics/protocol.png)
Plasma Renin Activity
The PRA was measured in specimens obtained from a venous cannula after 1 hour of supine rest and 15 minutes of tilt at 65 degrees. The PRA was measured by radioimmunoassay using the method of Waite.11

Plasma Felodipine Concentration
Blood samples were taken 2 hours after the morning dose of felodipine on each study day for estimation of plasma felodipine concentration using the method of Ahnoff.12

Statistical Methods
Formal tests of statistical significance were obtained using standard methods of analysis of variance. The SAB-HR reflex sensitivity results were analyzed after logarithmic transformation because the distribution of values was markedly skewed. In this instance, geometric means are reported together with geometric standard deviations (GM x/- GSD).

Three patients failed to complete the 6 week and 6 week + 1 day studies. Presentation of observed averages over the period of study could thus be affected by missing data from subjects with values that are systematically lower or higher than average. Therefore, all averages are presented over all subjects, and missing values were estimated using an SPSS-X commercially available computer program (SPSS, Chicago, IL, USA), which calculates the expected value from the analysis of variance. Tests of statistical significance for the 6 week and 6 week + 1 day studies were performed using only the data from the six patients who completed the study.

Results are expressed as the mean ± SD. Statistical significance is reported for $p$ levels less than 0.05.

Results
Casual Blood Pressures
Indirectly measured supine SBP and DBP were significantly reduced compared with placebo control values at the acute, 1 week, and 6 week assessments (Table 1). Heart rate was increased at the acute assessment but had returned to control levels by 1 week and 6 weeks and fell significantly below the 6 week level after withdrawal of active treatment and substitution of placebo at 6 weeks + 1 day.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 9)</th>
<th>Acute (n = 9)</th>
<th>1 week (n = 9)</th>
<th>6 weeks (n = 6)</th>
<th>6 weeks + 1 day (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>176 ± 16</td>
<td>152 ± 10*</td>
<td>159 ± 20†</td>
<td>153 ± 13†</td>
<td>168 ± 12‡</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>104 ± 5</td>
<td>90 ± 6§</td>
<td>93 ± 11‡</td>
<td>88 ± 12‡</td>
<td>100 ± 10‡</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>79 ± 7</td>
<td>82 ± 14†</td>
<td>71 ± 11</td>
<td>69 ± 12</td>
<td>64 ± 6§</td>
</tr>
</tbody>
</table>

Values are means ± SD. Control = during placebo treatment; acute = after first dose of felodipine; 6 weeks + 1 day = 24 hours after placebo treatment reinstated; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.

*p < 0.001, †p < 0.05, §p < 0.01, compared with control values; ‡p < 0.05, compared with values after 6 weeks.

Intra-arterial Blood Pressure and Duration of Action
Ambulatory intra-arterial blood pressure recordings demonstrated a reduction in overall SBP (control, 158 ± 28; 6 weeks, 139 ± 18 mm Hg) and DBP (control, 93 ± 16; 6 weeks, 83 ± 12 mm Hg) after 6 weeks of treatment with no significant change in heart rate (control, 75 ± 6; 6 weeks, 70 ± 6 beats/min). Hourly analysis showed that a clinically significant reduction of more than 10% in mean blood pressure occurred only between 3 and 9 hours after the orally administered dosage (Figure 2).

Blood Pressure Variability
Variability of SBP and DBP was unchanged after 6 weeks of chronic treatment (Figure 3).

Cardiovascular Reflexes
The SAB-HR reflex sensitivity did not change significantly at any stage, although there was a trend toward improvement at 6 weeks (control, 3.49 x/-H 1.42; acute, 4.19 x/-H 2.00; 1 week, 3.87 x/-H 1.73; 6 weeks, 6.00 x/-H 1.82; and 6 weeks + 1 day, 4.56 x/-H 1.82 msec/mm Hg). Figure 4 shows changes in the reflex set point throughout the study. With acute treatment it moved downward and to the left along the line of the sensitivity slope, indicating a fall in SBP ($p < 0.01$) with an increase in heart rate ($p < 0.01$) caused by deactivation of the SAB-HR reflex. At 1 week the set point had moved directly upward, indicating sustained blood pressure reduction with return of the heart rate to control values ($p < 0.05$) because of reflex resetting. There was no significant change in set point from 1 week to 6 weeks. Twenty-four hours after withdrawal of felodipine at 6 weeks + 1 day, the set point had moved upward and to the right, indicating an increase in SBP ($p < 0.05$) with a reduction in heart rate ($p < 0.05$) to below control levels caused by reactivation of the SAB-HR reflex at its reset level.

The blood pressure and heart rate responses to tilt are shown in Figure 5. Supine SBP and DBP were significantly lower at the acute, 1 week, and 6 week assessments ($p < 0.05$ for all) during active treatment than during placebo treatment at control and 6 weeks + 1 day. Heart rate increased with acute treatment ($p < 0.01$) but returned to control levels at 1 week and 6 weeks. There were no significant differences in the
SBP, DBP, and heart rate responses to tilt at any stage (Table 2).

Mean arterial pressure decreased significantly in all phases of Valsalva's maneuver at the acute, 1 week, and 6 week assessments (Figure 6) and returned to control levels at 6 weeks + 1 day. Heart rate was increased (p<0.01) in all phases at the acute assessment, but it was comparable to control at 1 week and 6 weeks, and significantly less than control after switching to placebo at 6 weeks + 1 day. The Valsalva ratio remained unchanged (control, 1.42 ± 0.20; acute, 1.45 ± 0.28; 1 week, 1.37 ± 0.20; 6 weeks, 1.35 ± 0.27; 6 weeks + 1 day, 1.32 ± 0.23).

Plasma Renin Activity

No significant changes were found in supine PRA throughout the study (control, 1.6 ± 1.1; acute, 1.9 ± 1.2; 1 week, 1.9 ± 1.2; 6 weeks, 1.8 ± 1.3; 6 weeks + 1 day, 1.6 ± 1.2 mmol/L plasma/hr). The

Figure 2. The hourly averaged ambulatory blood pressure (BP) and heart rate (HR) data from six patients obtained before treatment while taking placebo (solid lines) and after 6 weeks of chronic therapy (broken lines). The time of the evening dose of felodipine or placebo is shown by the vertical dashed line.

Figure 3. Waking and sleeping blood pressure variability in six patients before and after 6 weeks of chronic treatment with felodipine. No significant changes were seen in the variability of systolic (SBP) or diastolic blood pressure (DBP).

Figure 4. Mean changes in sinoatrial reflex set point throughout the study. The solid circles represent set points, and the slopes of the lines represent mean reflex sensitivity. The arrows show movement of the set point: Arrow 1, along the sensitivity slope because of reflex deactivation with acute treatment (n = 9); Arrow 2, directly upward because of baroreceptor reflex resetting by 1 week (n = 8); and Arrow 3, back along the sensitivity slope because of reflex activation after withdrawal of treatment (n = 6). PI = pulse interval; SBP = systolic blood pressure.
PRA on tilting was also unchanged (control, 1.8 ± 1.4; acute, 2.6 ± 2.1; 1 week, 2.1 ± 1.3; 6 weeks, 2.2 ± 1.3; 6 weeks + 1 day, 1.7 ± 1.1 mmol/L plasma/hr).

Weight and Ankle Circumference

There were no significant changes in weight (control, 76.2 ± 14.0; acute, 76.3 ± 13.7; 1 week, 76.4 ± 13.3; 6 weeks, 76.5 ± 13.4; 6 weeks + 1 day, 77.0 ± 13.5 kg) or ankle circumference (control, 23.0 ± 1.5; acute, 22.8 ± 1.3; 1 week, 22.7 ± 1.4; 6 weeks, 22.7 ± 1.5; 6 weeks + 1 day, 23.2 ± 1.4 cm) throughout the study.

**Table 2. Changes in Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate Caused by 15 Minutes of Tilt at 65 Degrees During Placebo, After the First Dose of Felodipine, After 1 and 6 Weeks of Active Treatment, and 24 Hours After Replacing Active Treatment with Placebo**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 9)</th>
<th>Acute (n = 9)</th>
<th>1 week (n = 8)</th>
<th>6 weeks (n = 6)</th>
<th>6 weeks + 1 day (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔSBP (mm Hg)</td>
<td>-1.0</td>
<td>-2.3</td>
<td>-2.7</td>
<td>-2.6</td>
<td>-2.5</td>
</tr>
<tr>
<td>ΔDBP (mm Hg)</td>
<td>+13.8</td>
<td>+14.5</td>
<td>+10.9</td>
<td>+11.9</td>
<td>+11.8</td>
</tr>
<tr>
<td>ΔHR (beats/min)</td>
<td>+13.0</td>
<td>+22.8</td>
<td>+15.6</td>
<td>+14.0</td>
<td>+11.8</td>
</tr>
</tbody>
</table>

There were no significant differences between groups. See Table 1 for key to abbreviations.

**Plasma Felodipine Estimations**

Plasma felodipine concentrations ranged from 5.1 to 10.4 nmol/L (mean, 6.3 ± 1.73 nmol/L) during active treatment phases, suggesting good patient compliance (therapeutic range, 5–10 nmol/L). Felodipine treatment was well tolerated, and no adverse effects were reported.

**Discussion**

Our results indicate that felodipine monotherapy reduced blood pressure significantly in hypertensive patients after a single dose, and this reduction was maintained during 6 weeks of therapy. Ambulatory intra-arterial pressure monitoring suggested that the clinically useful antihypertensive effect (>10% fall in mean arterial pressure) persisted for only 9 hours following an oral dose, indicating that this preparation of felodipine should be administered three times a day.

Acute administration was accompanied by an increase in heart rate caused by deactivation of the SAB-HR reflex. An increase in PRA was seen after acute treatment, but this did not reach statistical significance. However, such an increase, resulting from baroreceptor reflex activation of the sympathetic nervous system, would be expected and would be consistent with the experience of Luft et al. with a related calcium antagonist, nifedipine. It is also possible that the renin-angiotensin system could be stimulated by the transient natriuretic effect, which was seen immediately after initiating treatment.

We found that the SAB-HR reflex had reset after 1 week of treatment, with heart rate and PRA returning to control levels despite maintained hypotensive activity. This finding is consistent with our earlier work with other calcium antagonists in essential hypertension, although these studies did not examine baroreceptor reflex status so early in the course of chronic treatment. Twenty-four hours after therapy was withdrawn, we saw a significant reduction in heart rate to less than control levels, which was due to activation of the SAB-HR reflex at its new level. Further studies early in the course of treatment are required to determine exactly when resetting occurs in humans, but we have shown that it is complete 1 week after initiating treatment.

The mechanisms by which SAB-HR reflex resetting occurs are not understood, and in theory, any part of the reflex arc may be involved. The possibility of a
These findings are of clinical importance because combination of felodipine with β-adrenergic antagonists to reduce reflex tachycardia, as advocated by Hansson et al.,21 seems to be unnecessary. It may be that other vasodilators, such as minoxidil and hydralazine, do not require long-term concomitant β-blockade. This possibility requires further investigation.

We did not see statistically significant improvement in SAB-HR reflex sensitivity with chronic therapy, in contrast to earlier studies using nifedipine.1 However, our period of chronic treatment was considerably shorter (6 weeks as compared with 16 weeks), and it may be that the quantitative increase in sensitivity that we observed would reach significance with larger numbers of subjects and a longer treatment period.

The lack of quantitative changes in the responses to tilt and Valsalva’s maneuver and in blood pressure variability with felodipine treatment suggests that this drug does not impair reflex vasopressor responses to circulatory stress and therefore is unlikely to produce postural hypotension. In addition, the drug was well tolerated and did not produce fluid retention, as assessed by changes in weight and ankle circumference. We conclude that monotherapy with felodipine reduces blood pressure in essential hypertension without persistent tachycardia or sustained activation of the renin-angiotensin system.

Acknowledgments

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References

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FIGURE 6. Average mean blood pressure and heart rate response to Valsalva’s maneuver. A significant reduction in pressure occurred with acute (—•—•), 1 week (–○–○), and 6 weeks (**••••••) assessments when compared with control (—–—–) and 6 weeks + 1 day (○—○—○) assessments. Pulse interval was significantly shortened at the acute study and lengthened at 6 weeks + 1 day. Phase IIa = the lowest pressure in the first part of Phase II; Phase IIb = the peak of the rise occurring later in Phase II.
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