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The effect of felodipine on forearm haemodynamics and the myogenic response of the forearm resistance vessels in normal man

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1 The effect of felodipine 10 mg oral solution or placebo on peripheral haemodynamics and the response of the forearm resistance vessels to venous occlusion was studied in seven normotensive individuals.

2 Felodipine produced a significant fall in diastolic blood pressure (DBP max = −15 mm Hg), a rise in heart rate (heart rate max = +15 beats min^{-1}) (both $P < 0.01$), and an overall fall in calculated forearm vascular resistance (calculated forearm vascular resistance max = −19.6 units, $P < 0.001$).

3 Felodipine had no significant effect on the vasodilator response, but limited the vasoconstrictor response following venous occlusion.

4 These observations suggest that felodipine is a potent vasodilator and interferes with the myogenic response of vascular smooth muscle of the forearm resistance vessels.

Keywords vasodilatation myogenic response baroreflex felodipine

Introduction

Felodipine is a potent calcium antagonist with little negative inotropic effect (Culling *et al.*, 1984); in common with other agents of this group it is a vasodilator and potentially of use in the management of hypertension; it is recognised to have a considerable first pass metabolism by the liver (Edgar *et al.*, 1985). There is conflicting evidence of the effect of calcium antagonists on blood pressure in normotensive subjects, some studies demonstrating a fall in blood pressure (Millar *et al.*, 1983) and others no effect (MacGregor *et al.*, 1982; Lederballe Pedersen *et al.*, 1980).

Previous work from this department (Ireland *et al.*, 1983) has demonstrated a biphasic response of the forearm vasculature to venous occlusion; there is an initial vasodilator phase, which may be due in part to a myogenic response, and also probably due to accumulation of metabolites, followed by vasoconstriction, which we have shown to be independent of the autonomic nervous system, indicating that this is a reflex myogenic response of the vascular smooth muscle to stretch.

We have investigated the effect of felodipine on blood pressure, heart rate, forearm blood flow and the arterial response to venous occlusion in normal man.

Methods

Seven healthy male subjects took part in the study; their mean age was 30 ± 3 years (range 27–35 years) and mean ± s.d. resting blood pressure 103 ± 5/70 ± 5 mm Hg. All studies took place in the mornings, and smoking and coffee were forbidden on the day of the study. Each subject was studied on two separate occasions, at least 48 h apart, one study following the oral administration of felodipine solution 10 mg and the other following matching placebo. The order of administration was random and the study was single-blind.

Each subject rested supine for 30 min in a quiet room with a temperature maintained constantly at 28° C to minimise any effect of change in blood flow due to ambient temperature change,

and a venous cannula was inserted for blood sampling. A mercury in rubber strain gauge was used to measure blood flow in the left arm (Whitney, 1953). A 2" cuff was placed around the wrist to exclude circulation to the hand, and a 1" cuff placed around the upper arm to occlude venous return. Each cuff was connected via a 3-way tap to pressure reservoirs of 50 l capacity to ensure rapid inflation. One minute prior to recording the wrist cuff was inflated to 200 mm Hg. Venous occlusion was produced by inflation of the upper arm cuff to 100 mm Hg, which we have previously shown to cause a rise in mean venous pressure of 46 mm Hg (Ireland *et al.*, 1983). Ten recordings of blood flow were made over a 2–3 min period before administration of placebo or felodipine and at every 15 min thereafter for 120 min.

Plethysmographic blood flow records made after venous occlusion of the forearm show a biphasic response, initially vasodilator then vasoconstrictor. This response was measured by the method previously described by this department (Ireland *et al.*, 1983). Essentially this involves inflation of the upper arm cuff for 5 min with inflation of the wrist cuff after 4 min. Venous occlusion is released and flow measured at 5, 10, 20, 30 s and then every 15 s for 3 min. This response was measured before administration of felodipine or placebo, and then at 15, 30, 45, 60, 90 and 120 min thereafter. The blood flow was calculated for each observation after the release of the forearm venous occlusion and expressed as the relative blood flow by dividing this value by the resting blood flow.

Blood pressure was measured in the right arm using an 'Alp' UA101 semi-automatic sphygmomanometer to remove observer bias. Heart rate was estimated by palpation at the wrist. Measurements of blood pressure and heart rate were made before administration of felodipine or placebo, 5 and 15 min after and then every 15 min to 120 min.

Plasma felodipine levels were estimated by gas liquid chromatography with electron capture detection at Hassle AB, Molndal, Sweden (Anhoff, 1984), and were measured every 15 min for the first hour, and then at 90 and 120 min.

Vascular resistance was calculated by dividing the mean blood pressure by the resting blood flow and is expressed as arbitrary units.

Statistical analysis was by Student's *t*-test for paired data; blood flow characteristics were analysed by analysis of variance; the total variance for each variable was partitioned into sources of variance attributable to that between subjects, placebo *vs* felodipine, control *vs* subsequent times for both placebo and felodipine, between subsequent times for each drug and residual variance; hence each source of variation was tested for its statistical significance.

Results (Figure 1)

Blood pressure

Following placebo there was no significant change in systolic or diastolic blood pressure.

Following the administration of felodipine 10 mg at time 0, there was an initial slight increase in systolic and diastolic blood pressure at 5 min (statistically insignificant) but this was quickly followed by a statistically significant fall in diastolic blood pressure after 30 min which persisted to approximately 90 min. There was no significant change in systolic blood pressure.

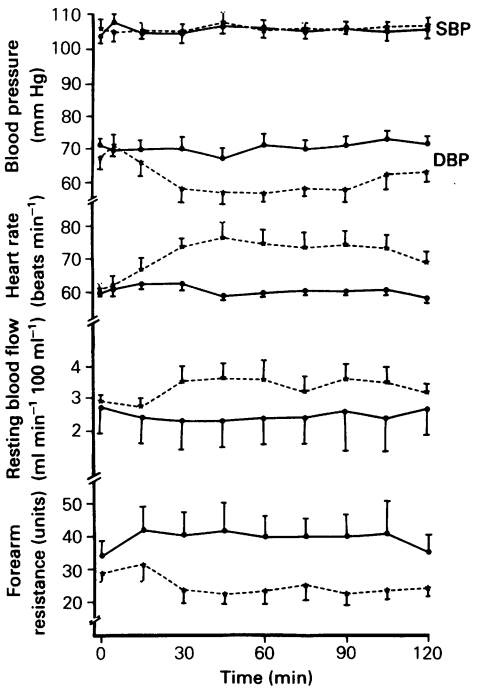

Figure 1 Mean systolic and diastolic blood pressure, heart rate, resting blood flow and forearm vascular resistance following administration of placebo (—) or felodipine (---). Results are shown as mean ± s.e. mean. Diastolic blood pressure and heart rate are statistically different between 30 and 90 min inclusive (all $P < 0.05$). Resting blood pressure and forearm resistance differ statistically overall by analysis of variance ($P < 0.001$).

Heart rate

Placebo produced no significant change in heart rate. Felodipine 10 mg induced an increase in heart rate in all seven subjects; this effect became statistically significant at 30 min and persisted until approximately 90 min.

Forearm blood flow and calculated vascular resistance

There was a large variation in resting blood flow between subjects, this was statistically significant by analysis of variance ($P < 0.005$). There was no statistically significant difference between control (time zero) blood flows before administration of felodipine or placebo. There was no statistically significant change in resting blood flow or calculated vascular resistance induced by placebo.

Following felodipine administration there was a rise in forearm blood flow. This change was seen first at 30 min. The mean ± s.d. 60 min value for placebo was 2.4 ± 1.1 and for felodipine was 3.6 ± 1.6 ml min^{-1} 100 ml^{-1}. Overall felodipine produced a statistically significant rise in resting blood flow compared with placebo ($P < 0.001$).

Calculated vascular resistance fell, and overall there was a statistically significant difference between resistance following the administration of placebo and felodipine ($P < 0.001$).

Arterial response to venous occlusion: (Figure 2)

1. Maximum blood flow—vasodilatation following venous occlusion—was less following felodipine administration though this did not reach statistical significance.
2. Minimum blood flow—vasoconstriction following venous occlusion—achieved after felodipine was not as low as that after placebo. Relative minimum blood flow at 60 min (mean ± s.d.) was 0.4 ± 0.1 after placebo and 0.7 ± 0.2 s.d. after felodipine; overall there was a statistically significant increase in minimum blood flow following felodipine ($P < 0.001$); i.e the degree of vasoconstriction was less.

Plasma felodipine concentrations

Figure 2 shows the mean plasma levels for all subjects. Absorption was rapid and the level began to fall after approximately 60 min. There was considerable inter-subject variation in the plasma levels of felodipine—presumably due to the variation in first pass metabolism (Edgar *et al.*, 1985). Figure 2 also shows how the relative minimum blood flow rose with plasma felodipine concentration. There was a correlation between $\log_{10}$ individual plasma concentration and the relative minimum blood flow; $n = 40$, $r = 0.455$, $P < 0.01$. There was also a correlation between mean absolute heart rate and $\log_{10}$ plasma felodipine concentration, $n = 6$, $r = 0.79$, $P < 0.05$.

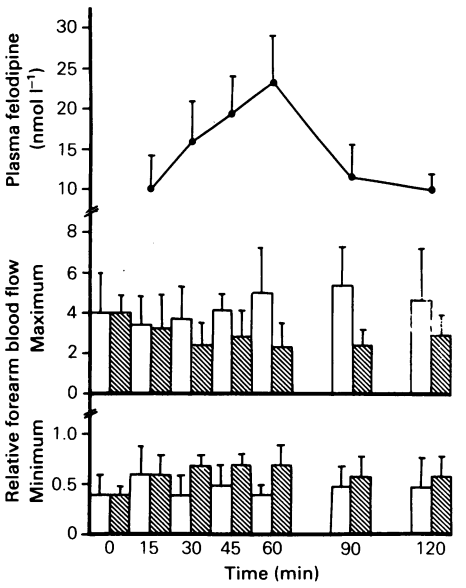

Figure 2 Plasma felodipine concentration and relative maximum and minimum blood flow following administration of placebo □ or felodipine ▨. Results are shown as mean ± s.d.

Discussion

Our observations indicate that felodipine is a vasodilator which alters the myogenic response of vascular smooth muscle. Within 30 min of taking the drug there was a significant fall in arterial pressure and forearm vascular resistance accompanied by reflex increases in heart rate and peripheral blood flow.

We have previously demonstrated that the brief period of vasoconstriction that follows venous occlusion of the forearm is the result of a myogenic response of the vascular smooth muscle independent of the autonomic nervous system. This response is consistent and reproducible as can be seen in the observations following placebo (Figure 2). Within 30 min of taking felodipine there was a significant change in this response which was diminished as reflected by a lesser degree of vasoconstriction (Figure 2). This

altered response is consistent and reproducible, and maintained for 30–60 min. There is also a correlation between this and the individual $\log_{10}$ plasma felodipine concentrations. Our observations are consistent with calcium slow channel blockers altering the excitation contraction coupling within the vascular smooth muscle such as to impair its response to stretch. This may be the method whereby felodipine brings about vasodilatation.

The vasodilator response of the forearm vessels to brief venous occlusion is much more variable as is reflected in both phases of this study. Following felodipine there was a tendency for the vasodilator response to be less, paralleled with an increase in resting forearm flow (as a result of vasodilatation). The likeliest explanation for this observation is that with a vasodilator on board, further capacity for vasodilation is reduced. This observation on the vasodilator phase compares with our previous observations of vasodilatation following autonomic blockade when we noted that maximum blood flow following venous occlusion was increased compared with placebo. This provides further evidence that vasodilatation is in part under myogenic control (Caro *et al.*, 1970) though we believe that several other factors influence this response including overall sympathetic tone, local environmental conditions (Po_2, pH etc.) and hypertrophy of the smooth muscle itself (Littler & Ireland, 1985).

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