Effects of felodipine on atrial natriuretic peptide in hypertensive non-insulin dependent diabetes mellitus

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Eighteen patients with non-insulin dependent diabetes mellitus and hypertension were treated during two 4 week periods with the calcium antagonist felodipine or placebo in a double-blind, randomised, cross-over study. Mean systemic blood pressure was significantly lower on felodipine, without producing a deleterious effect on diabetic control. Felodipine was associated with an increment in plasma renin concentration but plasma aldosterone and the renal outputs of sodium and dopamine were similar on both treatments. Plasma atrial natriuretic peptide levels were significantly reduced following felodipine treatment.

Keywords calcium antagonist felodipine non-insulin dependent diabetes mellitus plasma ANP

Introduction

Non-insulin dependent diabetes mellitus (NIDDM) is associated with a high incidence of hypertension which increases both micro- and macro-vascular complications (Tuck, 1988). Traditional first line antihypertensive agents may not be ideal in the treatment of diabetic patients and attention has been focused on use of the newer calcium antagonists and angiotension converting enzyme inhibitors. Plasma atrial natriuretic peptide (ANP) levels may be elevated in diabetes associated with hypertension (Giorgino *et al.*, 1989), although the response following calcium antagonism is unknown. In a recent study, felodipine, a second generation dihydropyridine calcium antagonist was shown to be effective in the treatment of hypertension in NIDDM, without significantly altering glucose tolerance or lipid profiles (Capewell *et al.*, 1989). Eighteen of these patients therefore formed the basis of the present study which sought to characterise the systemic and renal hormonal response to felodipine treatment.

Methods

Eighteen patients with NIDDM with a mean disease duration of 6 years (range 1–17 years)

were studied. There were 12 males and six females, mean age range 61 years (range 46–73 years), mean body weight 82 kg (range 54–104 kg). All patients were hypertensive with a mean duration of 8 years (range 1–16 years) and receiving antihypertensive treatment. Serum creatinine was less than $160 \mu\text{mol l}^{-1}$ in all patients, three had intermittent and one persistent microalbuminuria. Six patients were controlled by diet alone and 12 required oral hypoglycaemic agents (metformin-9, chlorpropamide-2, glipizide-1). Antihypertensive medication was discontinued before a 'wash-out' period of 2–4 weeks. Subjects were entered into the study if a diastolic blood pressure of 95–115 mm Hg was reached during this period. Patients were then randomised, in double-blind fashion, to either 4 weeks of active felodipine followed by 4 weeks of placebo, or *vice versa*. Felodipine or placebo was commenced at 5 mg twice daily, and patients assessed fortnightly. If diastolic pressure remained at or above 95 mm Hg the dose was increased to 10 mg twice daily. Normal diet and oral hypoglycaemic therapy were continued and no other medications were permitted. Systolic and diastolic (phase V) blood pressures were recorded after 5 min rest, sitting, using a Hawksley random zero sphygmomanometer.

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Patients were trained to collect 24 h urine samples at the end of each treatment period. At each visit blood was withdrawn for estimation of plasma hormones after sitting quietly for 20 min. Blood sampling was performed around 09.00 hours in all cases to account for diurnal variation.

Urine dopamine was assayed following extraction on alumina (Anton & Sayre, 1964) by high performance liquid chromatography and electrochemical detection (Jeffrey *et al.*, 1987). Plasma atrial natriuretic peptide (ANP) was measured by radioimmunoassay after extraction on Sep-Pak C₁₄ cartridges (Freestone *et al.*, 1989). Plasma renin concentration (PRC) was measured by the method of Millar *et al.* (1980) and plasma aldosterone by radioimmunoassay (Fraser *et al.*, 1973).

Results are expressed as means $\pm$ s.e. mean. Data were analysed by Student's *t*-test for paired samples. Linear regression analysis was used to determine the correlation between variables. The study was approved by local Ethics Subcommittee and written consent was given by each patient.

Results

At the end of the wash-out period, prior to randomisation, mean systemic blood pressure was 175/103 mm Hg. Felodipine treatment was associated with an appreciable and significant

reduction in mean systemic pressure, compared with placebo. Mean pulse rates were not significantly different (Table 1). There was no significant difference in fasting blood glucose or HbA₁ values, nor in the 24 h excretion of sodium and dopamine. Plasma aldosterone levels were also similar. PRC was significantly higher on felodipine ($P < 0.05$) (Table 1). Figure 1 depicts the individual and mean values for plasma ANP. There was a marked reduction associated with felodipine treatment, apparent in 15 of the 18 patients ($P < 0.01$). There was no significant correlation between the decrement in mean arterial pressure and the reduction in plasma ANP ($r = 0.22$, $P > 0.1$).

Discussion

Over the 4 week period of study, felodipine proved effective as monotherapy in the treatment of hypertension associated with NIDDM. The drug does not appear to affect adversely glucose tolerance or lipid profiles and may have useful therapeutic potential in such patients (Capewell *et al.*, 1989). Hypertension in NIDDM is likely to represent a heterogeneous condition and various aetiological factors have been proposed including, the presence of co-existing essential hypertension, obesity, enhanced vascular reactivity, increased extracellular fluid volume and hyperinsulinaemia (Tuck, 1988).

Table 1 Systemic and renal parameters in 18 patients following treatment with placebo or felodipine. Values are means $\pm$ s.e. mean

	Placebo	Felodipine	Significance
Mean arterial pressure (mm Hg)	166/102 $\pm 5/2$	147/88 $\pm 3/2$	$P < 0.01$
Pulse rate (beats min ⁻¹)	79 ± 3	82 ± 3	NS
Urine sodium excretion (mmol 24 h ⁻¹)	178 ± 21	194 ± 20	NS
Urine dopamine excretion (nmol 24 h ⁻¹)	1338 ± 113	1340 ± 116	NS
Plasma atrial natriuretic peptide (pg ml ⁻¹)	73.1 ± 9.1	48.6 ± 5.8	$P < 0.01$
Plasma renin concentration (μ u ml ⁻¹)	17.0 ± 3.1	26.9 ± 5.5	$P < 0.05$
Plasma aldosterone (ng ml ⁻¹)	7.2 ± 0.7	7.8 ± 1.0	NS
Fasting blood glucose (mmol l ⁻¹)	9.4 ± 0.7	10.0 ± 0.7	NS
HbA ₁ (%)	9.5 ± 0.5	9.3 ± 0.5	NS

Figure 1 Plasma ANP response to placebo and felodipine. Individual values are plotted with means $\pm$ s.e. mean; * $P < 0.01$.

Giorgino *et al.* (1989) have recently reported that plasma ANP was elevated in hypertensive patients with NIDDM compared with controls, which may be compatible with an expanded extracellular fluid space in such patients. No control group was available from the present study though the mean baseline value for ANP was at the upper end of the range for our laboratory, drawn from healthy young subjects.

An interesting result of the present study was the marked reduction in plasma ANP following treatment with felodipine. The mechanism has not been elucidated but a number of possibilities exist. Firstly calcium channel blockers may have a direct action on ANP synthesis or release. *In vitro* studies suggest that ANP secretion is a calcium-dependent process (Saito *et al.*, 1986). *In vivo*, Haufe *et al.* (1988) demonstrated in man that verapamil blocked ANP release induced by an increase in right atrial pressure. However, this has to be reconciled with the results of other studies in essential hypertension in which

nifedipine acutely stimulated plasma ANP (Iwasaki *et al.*, 1989; Rappelli *et al.*, 1989).

Secondly, calcium antagonists may influence salt and water homeostasis and hence ANP release. Felodipine certainly exerts an acute natriuretic action (Hulthen & Katzman, 1988). Pevahouse *et al.* (1987) have provided evidence for a sustained natriuresis following 6 weeks treatment with nifedipine in essential hypertension. On withdrawal of therapy, subjects went into positive sodium balance with increase in body weight, and a rebound increase in plasma ANP. In the present study sodium excretion was similar on placebo and felodipine: this is to be expected as a new steady state would be reached during treatment whereby input matches output. Renal dopamine excretion correlates with prevailing salt status (Oates *et al.*, 1979) and the close similarity in dopamine output on placebo and treatment argues against a prolonged reduction in exchangeable body sodium. However subjects were not studied under metabolic balance conditions and a small change in dopamine excretion may have been obscured by background variability. The increase of PRC probably reflects baroreceptor-mediated sympathetic drive consequent upon the hypotensive response (Hulthen & Katzman, 1988).

Thirdly, the decline in ANP may result directly from the reduction in systemic blood pressure and a decline in atrial tension. Zachariah *et al.* (1987) demonstrated a reduction in plasma ANP following 6 weeks treatment with nitrendipine in essential hypertensives. This does not appear to be a specific effect of calcium antagonism. Sugawara *et al.* (1988) treated a group of essential hypertensives with various antihypertensive agents and reported a significant reduction in plasma ANP over 3 months. In contrast to the present study, there was a significant correlation between the decrement of plasma ANP with the fall in mean arterial pressure.

The significance of the reduction in plasma ANP after treatment remains unclear. Further studies are required to elucidate the biological role of the peptide in diabetes and hypertension, beneficial or otherwise. It remains to be seen whether the monitoring of ANP levels in such patients will in future prove clinically useful in assessing the adequacy of blood pressure control.

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