Studies with fenoldopam, a dopamine receptor DA₁ agonist, in essential hypertension

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1 A series of studies were undertaken to assess the effect of oral fenoldopam, a specific DA₁ dopamine receptor agonist on blood pressure and renal function in patients with mild essential hypertension.

2 Six patients with essential hypertension were entered into a dose-ranging study and received either placebo, 25, 50 or 100 mg fenoldopam. A significant, dose-related reduction in diastolic blood pressure, and increase in heart rate was demonstrated (both $P < 0.05$), maximal at 45 min to 1 h. Fenoldopam increased plasma renin activity.

3 In a double-blind study, seven patients received a single dose of fenoldopam 100 mg or placebo. Fenoldopam produced a significant fall in systolic ($P < 0.05$) and diastolic ($P < 0.01$) blood pressure and renal vascular resistance ($P < 0.01$). Urine flow rate ($P < 0.05$), sodium excretion ($P < 0.01$), plasma renin activity ($P < 0.05$) and plasma aldosterone ($P < 0.05$) increased.

4 Five patients underwent measurement of the above parameters following a single dose of fenoldopam 100 mg with a repeat of these measurements after they had taken fenoldopam 100 mg four times daily for 1 month. The acute response of blood pressure to the single dose appeared unchanged but tachyphylaxis was evident in the responses of heart rate, plasma renin activity and plasma aldosterone.

Keywords fenoldopam dopamine hypertension renal function

Introduction

Homer Smith's group first demonstrated that there is renal vasoconstriction in patients with essential hypertension (EH) (Goldring *et al.*, 1941). This abnormality may be part of a generalised increase in vascular resistance or, more likely, may be of particular significance in regard to the development of the condition. The renal vasoconstriction is present early (Hollenberg *et al.*, 1978) and appears to selectively affect the cortical nephrons (Britton, 1981). Receptors specific for dopamine exist in the renal vasculature through which exogenous dopamine mediates vasodilatation (Goldberg, 1972).

Dopamine is also a natriuretic substance (McDonald *et al.*, 1964). Orally active analogues of dopamine might be of particular value in EH; this paper describes studies with one such compound: fenoldopam.

The most widely used classification of dopamine receptors is that of Goldberg & Kohli (1979). Dopamine receptors in the peripheral vasculature are held to be of DA₁ type. Dopamine receptor agonists (apomorphine, bromocriptine) have been available for some time but are active predominantly at DA₂ receptors. The development of benzazepine derivatives

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such as fenoldopam (6-chloro-7, 8-dihydroxy-1-(*p*-hydroxyphenyl)-2,3,4,5-tetrahydro-(1H)-3-benzazepine methane sulphonate) which appears to be a specific agonist at the DA₁ receptor (Hahn *et al.*, 1982; Ackerman *et al.*, 1983) is therefore an important advance. Fenoldopam does not cross the blood brain barrier in rats (Hahn *et al.*, 1982) unlike some other closely related benzazepines (Weinstock *et al.*, 1983) probably because of polar groups on the molecule (Figure 1). Previous studies have shown a pronounced renal vasodilator and modest hypotensive effect in normal man (Harvey *et al.*, 1985). The renal vasodilator effect is antagonised by metoclopramide (Stote *et al.*, 1983). The present studies were undertaken to investigate the effect of fenoldopam on blood pressure (BP) and renal function in patients with mild essential hypertension.

Methods

Patients and protocols

All patients had a supine BP of 150/95 mm Hg or greater (Korotkov phase V for diastolic pressure) when measured by standard mercury sphygmomanometer on at least three separate occasions. Detailed investigation of renal function had not been undertaken prior to study in the absence of specific indications but all patients had a normal plasma creatinine concentration. Age at recruitment was 22–60 years and all had been either untreated or off medication for at least 4 days prior to study. Studies in any given patient were separated by at least 4 days. All protocols were approved by the Ethics Committee of the General Infirmary at Leeds.

Dose ranging study Six patients (age 45.4 ± 6.0 years, weight 67.6 ± 6.4 kg; mean $\pm$ s.e. mean) were given placebo, 25, 50 or 100 mg fenoldopam on four separate mornings. After 10 min supine rest baseline BP and pulse rate readings were made, then venous blood was taken to determine plasma renin activity (PRA) and plasma aldosterone (PA). Drug or placebo (single blind, in the above order) was then administered. BP and pulse rate measurements were taken in duplicate, supine and erect (after standing for 2 min) every 15 min for 4 h. A second blood sample for PRA and PA was taken at 1 h.

Study of the effect of a single dose of 100 mg fenoldopam on renal function Seven patients (age 44.3 ± 4.4 years, weight 80.8 ± 6.5 kg) were studied on two days being given fenoldopam 100 mg on one and placebo on the other according to a randomised double-blind protocol. The protocol for this section was identical to our studies with normal subjects (Harvey *et al.*, 1985) but with the addition of urine uric acid determinations. Briefly, urine for measurement of volume, sodium, potassium and uric acid excretion was collected for 2 h before, and from 0–2 and 2–4 h after administration of drug or placebo. Venous blood for PRA and PA was collected immediately before and 1 and 3.5 h after administration of drug or placebo. Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were measured over the period from 0.5–2 and 2–3.5 h after drug or placebo. BP and pulse were measured at 15 min intervals throughout.

Study of the effect of 1 month's therapy with fenoldopam Five subjects (age 38.7 ± 5.2 years, weight 73.0 ± 9.0 kg) had their BP and renal function measured according to the above protocol, being given 100 mg fenoldopam. They

Figure 1 Molecular structures of dopamine and fenoldopam.

then took fenoldopam 100 mg four times daily for a month and the laboratory study was repeated. Between the two study days patients were seen at home at weekly intervals.

A full blood count, differential white count, plasma electrolytes, urea, creatinine, uric acid, transaminases, lactic dehydrogenase, γ -glutamyl transferase and urinalysis were checked before and after each study day in the renal function study and before and after the 1 month treatment.

Methodology

BP was measured throughout using a Dinamap monitor (Critikon Ltd).

ERPF and GFR were measured using I^{125} orthoiodohippurate and Cr^{51} ethylene diamine tetra-acetic acid respectively by a modification of the single injection technique of Harries *et al.* (1972) which we described previously (Harvey *et al.*, 1985). Isotope excreted in a given time period is divided by the area under the plasma concentration curve in that period. The area under the curve (AUC) was calculated using a computer programme which drew straight lines between the points. This method of calculation of AUC was considered to give rise to no greater error than any other. All ERPF and GRF results were corrected to 1.73 m^2 body surface area using a standard nomogram. Renal vascular resistance (RVR) was derived from mean arterial pressure divided by renal blood flow.

PRA was measured by radioimmunoassay using a modification of the method of Haber *et al.* (1969). The intra and interassay coefficients of variation (CV) in our laboratory were 5.5% and 7.1% respectively. Specimens for PA were assayed using a kit produced by Diagnostic Products Corporation. Most of the specimens were assayed in one batch which had an intra-assay CV of 6.0%.

The AUC for all BP and heart rate (HR) responses was calculated and analysed using an analysis of covariance model that fits patients and treatments as main effects using baseline readings as covariate, i.e. takes account of between subject variation in baseline BP. This method produces adjusted mean AUC values which were compared with placebo at each dose level. A test of linearity of the trend of adjusted mean vs log dose was carried out for the dose levels 25, 50, and 100 mg. Our previous work demonstrated that the effect of fenoldopam on BP and HR occurs mainly in the first 2 h after oral dosing and so in the dose ranging study a decision was taken to analyse the 0–2 h and 2–4 h periods separately. In the renal function study

BP and HR measurements were analysed in two sections: before oral dosing and 0–4 h after dosing. Urinary parameters, renal haemodynamic measurements (ERPF, GFR, RVR), PRA and PA were analysed using an analysis of covariance taking account of patient, treatment and period, with baseline as a covariate. In the dose ranging study PRA and PA values were log transformed to stabilize the variance.

Results

Dose ranging study At all doses both supine systolic (SBP) and diastolic BP (DBP) showed a clear fall after fenoldopam which was greater than after placebo (Figure 2). The maximum effect was seen at 45 min or 1 h. Mean supine BP fell (after subtracting the fall after placebo) by 6.8/8.2, 12.5/13.0 and 13.6/16.9 mm Hg after the 25, 50 and 100 mg doses of fenoldopam respectively. The fall in erect BP was 0.9/5.3, –0.8/14.4 and 1.2/13.9 mm Hg respectively; i.e. erect SBP showed almost no change, with even a small increase after the 50 mg dose. When compared with placebo over 0–2 h and 2–4 h, the effect of fenoldopam on supine and erect SBP was not statistically significant at any dose. The AUC of SBP did not correlate with log dose. However, statistical analysis did show a significant effect on supine DBP (0–2 h) at the 50 and 100 mg doses (both $P < 0.05$) and there was a linear relationship between AUC (0–2 h) and log dose ($P < 0.05$). The linearity indicated a real reduction in BP at the 25 mg dose. Analysis did not demonstrate that the differences between the effects of the three different doses of fenoldopam were significant. Analysis of the erect DBP data showed a similar pattern. There was no evidence of postural hypotension.

Administration of fenoldopam is known to produce a tachycardia (Harvey *et al.*, 1985) and did so in this study also (Figure 3). There were significant supine pulse rate increases (0–2 h) at 50 mg and 100 mg ($P < 0.05$) and the increase after 25 mg was almost significant. The erect pulse rate data showed a similar pattern with a significant linear relationship between AUC (0–2 h) and log dose ($P < 0.05$). The PRA results also appeared to show a dose response relationship (Figure 4) although statistical support for such a relationship was not obtained. A statistically significant increase ($P < 0.05$) occurred at the 50 and 100 mg doses. PA did not show any significant changes.

Fenoldopam and renal function study BP fell and HR increased after fenoldopam (Figure 5). The data from drug administration to 4 h

Figure 2 Supine systolic and diastolic blood pressure after placebo (●—●), and 25 (●), 50 (○) and 100 (▲) mg of fenoldopam.

afterwards when compared with placebo showed significant changes in SBP ($P < 0.05$), DBP ($P < 0.01$) and pulse rate ($P < 0.05$).

Over the period 0.5–2 h after dosing ERPF was 373 ± 28 after placebo compared to $461 \pm 33 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ after fenoldopam,

Figure 3 Erect and supine pulse rate after placebo (●—●), 25 (●), 50 (○) and 100 (▲) mg of fenoldopam.

Figure 4 Plasma renin activity and plasma aldosterone immediately before, and after placebo, 25, 50 and 100 mg of fenoldopam (mean $\pm$ s.e. mean).

not quite attaining significance (Figure 6). During the period 2–3.5 h ERPF was only marginally greater after fenoldopam (272 ± 29) than after placebo (245 ± 29). Over both time periods, GFR was slightly greater after fenoldopam (90.1 ± 8.0 vs 86.3 ± 7.8 and 94.2 ± 9.9 vs 84.7 ± 8.9 respectively) but not significantly so. Fenoldopam reduced renal vascular resistance in all subjects, from 0.19 ± 0.02 after placebo to 0.13 ± 0.01 mm Hg min ml⁻¹ after fenoldopam ($P < 0.01$).

Compared with placebo, fenoldopam increased urine flow rate at 0–2 h ($P < 0.05$) and had a significant natriuretic effect at 0–2 and 2–4 h (both $P < 0.05$). Other than when cannulae were flushed with saline (2 ml after each sample) subjects received no sodium during the 6 h of the experiment. After placebo the expected fall in sodium excretion was seen but after fenoldopam there was an increase which was sustained. Fenoldopam increased the fractional excretion of sodium from $0.76 \pm 0.11\%$ to $1.12 \pm 0.20\%$ during the first 2 h; and from $0.58 \pm 0.12\%$ to $1.05 \pm 0.18\%$ during the second 2 h period

(Figure 7). The changes in fractional excretion of sodium were not statistically significant. Urinary potassium and uric acid excretion were also measured (not shown) and showed very little difference after fenoldopam. PRA increased ($P < 0.05$) from 1.4 ± 0.3 to 3.0 ± 0.8 ng angiotensin I h⁻¹ ml⁻¹ at 1 h. PA increased ($P < 0.05$) from 385 ± 63 to 505 ± 86 pmol l⁻¹ at 1 h (Figure 8).

Study of the effect of 1 month's therapy with fenoldopam After 1 month's therapy, baseline BP measurements (prior to fenoldopam) were lower (Figure 9). The mean reduction was 4.2/4.1 mm Hg. Fenoldopam produced an acute fall in BP as before and this effect was not attenuated by 1 month of treatment. The increase in HR, PRA and PA produced by acute administration of fenoldopam appeared less after 1 month of treatment with the drug (Figure 10).

A sixth subject (female, age 60 years, weight 76.2 kg) was entered in the 1 month therapy but had to be withdrawn after symptomatic hypotension on the first study day. Her BP dropped from 160/100 to 80/50 mm Hg for 10–15 min. There were no features of an allergic reaction and the time course of the hypotension suggested excessive sensitivity to the usual effect of fenoldopam.

A number of patients had noticed a sensation of facial warmth and flushing after fenoldopam when specifically questioned but the phenomenon was generally of mild intensity. The haematological and biochemical parameters monitored for safety showed no change after fenoldopam.

Discussion

Fenoldopam has a moderate but indisputable hypotensive effect. Statistical analysis confirmed that the changes in DBP and HR were dose dependent. It seems likely that only the greater inter-subject variation in supine SBP and PRA responses prevented confirmation of a dose-response relationship in these parameters also. Compared with our studies in normal subjects (Harvey *et al.*, 1985) the effect on BP appears to be proportionately greater in the hypertensive subjects. The mechanism involved in producing the fall in BP is not entirely clear since dopamine itself does not produce a fall in systemic pressure in man at doses which are renal vasodilator (McDonald *et al.*, 1964). The explanation may be that low doses of dopamine produce α -adrenoceptor mediated vasoconstriction in some vascular beds, e.g. the femoral

Figure 5 Blood pressure and pulse rate after placebo (○--○) and fenoldopam 100 mg (●—●).

Figure 6 Single dose and chronic dosing studies of fenoldopam: renal function (ERPF, GFR and RVR) measured 30–120 min after placebo or fenoldopam, and after fenoldopam before and after 1 month's therapy.

and carotid circulations (Eble, 1964). After prior α -adrenoceptor blockade, dopamine has a pronounced hypotensive effect (Goldberg, 1972). *In vivo* studies indicate that fenoldopam has agonist activity only at DA₁ receptors (Hahn *et al.*, 1982) but binding studies have shown affinity for α_2 -adrenoceptors and weak affinity for α_1 receptors (Foley & Sarau, 1984).

ERPF increased by 23.6% after fenoldopam which is less than the increase of 58.6% seen in the normal subjects (Harvey *et al.*, 1985). RVR fell by more in the normotensive subjects (38%) than in the hypertensive subjects (31%). GFR showed a variable response but increased in a majority of subjects. It appears that fenoldopam tends to correct the renal haemodynamic abnormalities in EH. The changes in renal perfusion and GFR are not greater in the hypertensives as might be expected if a deficiency of renal dopamine was present (Harvey *et al.*, 1984). However, the renal vasculature may be less responsive to vasodilators when EH is established, perhaps due to secondary arterial disease.

Dopamine is a potent natriuretic agent (McDonald *et al.*, 1964) and the effects of a putative dopamine receptor agonist on sodium excretion are therefore of considerable interest. These studies show only a small but significant natriuretic effect, but this was greater than in our studies in normal volunteers where no significant

Figure 7 Urine flow rate and sodium excretion after placebo (□) and fenoldopam (■) (mean + s.e. mean).

effect was demonstrated. Direct comparison with the normal volunteer studies cannot be made as neither study was performed under metabolic balance conditions, although the same protocol was used. It seems likely that the direct hypotensive effect together with stimulation of renin and aldosterone secretion could counter any direct natriuretic effect on the kidney, nevertheless, the small natriuretic effect we demonstrated may be clinically useful since other vasodilators have a tendency to produce salt and water retention. Fractional excretion of sodium increased after fenoldopam but not significantly, suggesting that an effect on tubular function independent of GFR might be present.

Figure 8 Plasma renin activity and plasma aldosterone after placebo (○) and fenoldopam 100 mg (●) (mean ± s.e. mean).

Dopamine receptors have been demonstrated on tubular cells (Bello-Reuss *et al.*, 1982) but a redistribution of intra-renal blood flow (Hardaker & Wechsler, 1973) might produce a similar effect. Uric acid excretion was measured in an attempt to provide corroborative evidence for a direct tubular effect; however, no changes were seen. This result is in contrast to that of Stote *et al.* (1983) who did observe an increase in the fractional excretion of uric acid.

The study of 1 month's therapy indicates that single doses of fenoldopam retain their hypotensive effect over this period. We found no suggestion of tachyphylaxis in the acute response of BP. After 1 month's treatment with fenoldopam the baseline DBP measurements appeared lower although subjects had not received fenoldopam since the previous evening. In the absence of a placebo group we cannot draw firm conclusions from this pilot study and a double-blind placebo controlled chronic study is clearly needed. Our data suggest that there might be tachyphylaxis evident in the HR, PRA and PA responses, which would be of benefit.

Figure 9 The response of blood pressure and pulse rate to fenoldopam 100 mg before (●—●) and after (○--○) 1 month's therapy with fenoldopam 100 mg four times daily.

Figure 10 The response of plasma renin activity and plasma aldosterone to fenoldopam 100 mg before (●—●) and after (○--○) 1 month's therapy with fenoldopam 100 mg four time daily (mean $\pm$ s.e. mean).

One other study of fenoldopam in the treatment of EH has recently been reported (Carey *et al.*, 1984). The results were broadly similar to those in the present study in that fenoldopam had an acute hypotensive effect and increased HR, PAH clearance and sodium excretion (but under sodium balance conditions). The hypotensive effect was maintained after 3 weeks therapy with fenoldopam 100 mg four times daily.

Fenoldopam has shown itself to be hypotensive and renal vasodilator in these limited studies in man. Whether it will be effective in the long term management of hypertension remains in doubt because of its short duration of action and its capacity to evoke renin release. However, the development of this compound points the way forward towards alternative DA₁ agonists which do not share the 3,4-dihydroxy benzene ring structure and can therefore avoid high first pass metabolism via sulphation and glucuronidation, the common fate of molecules possessing the basic structure of a catecholamine.

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