The effect of oral fenoldopam (SKF 82526-J), a peripheral dopamine receptor agonist, on blood pressure and renal function in normal man

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1 The effect of a single oral dose of 100 mg of fenoldopam on renal function and blood pressure was investigated in seven healthy male subjects in a double-blind placebo controlled study.

2 Mean diastolic blood pressure fell by 10 mm Hg, 45 min after oral dosing and then gradually returned to baseline values. There was an increase in pulse rate and a delayed rise in systolic blood pressure.

3 Measured from 30 to 120 min after drug ingestion, mean effective renal plasma flow increased to 158% of the value observed after placebo; mean glomerular filtration rate rose to 109% of the placebo value. Measured from 120 to 210 min after administration of the drug, effective renal plasma flow and glomerular filtration rate had returned to baseline values.

4 Fenoldopam produced a small increase in the mean sodium excretion rate which was not significantly different from the fall after placebo. No change was detected in urine flow or potassium excretion rate.

5 Mean plasma renin activity increased three-fold 1 h after oral dosing. Plasma aldosterone did not show a parallel increase although the plasma concentration at 1 h was significantly higher than after placebo.

6 The results show a pronounced renal vasodilator effect lasting about 2 h. The findings are consistent with marked DA₁ receptor agonist activity.

Keywords fenoldopam (SKF 82526-J) dopamine renal blood flow blood pressure

Introduction

It is well established that specific receptors for dopamine are present in the central nervous system, pituitary lactotroph cells and the peripheral vasculature (Kebabian & Calne, 1979). Two categories of receptor are distinguished and have been designated DA₁ and DA₂ (Goldberg & Kohli, 1983). Both types of receptor mediate vasodilatation in certain vas-

cular beds. DA₁ receptors are found on the smooth muscle cells of arterioles and are linked to adenylyl cyclase. DA₁ receptors are present in the renal and mesenteric vascular beds (Yeh *et al.*, 1969) and perhaps the coronary (Lang & Woodman, 1982) and cerebral circulations (Leenders *et al.*, 1984). DA₂ receptors are found on the pre-synaptic membranes of sym-

pathetic neurones where they inhibit nor-adrenaline release (Langer, 1974).

Fenoldopam (SKF 82526-J) is a benzazepine derivative (Figure 1) designed to have activity at DA₁ receptors. Hahn *et al.* (1982) showed that fenoldopam stimulates the dopamine sensitive adenylyl cyclase of rat caudate nucleus *in vitro* but has no behavioural effects in the intact animal indicating that fenoldopam does not cross the blood-brain barrier. The same investigators demonstrated that fenoldopam has relatively little effect on α - and β -adrenoceptors *in vitro* but has potent renal vasodilator activity in the anaesthetised dog. This haemodynamic effect was not attenuated by phenoxybenzamine, propranolol, atropine, mepyramine plus meti- amide, meclofenamic acid or reserpine but was inhibited by metoclopramide and bulbocapnine. Ackerman *et al.* (1983) showed that pretreat- ment with reserpine does not abolish the hypotensive effect of fenoldopam in the spon- taneously hypertensive rat indicating that fen- oldopam is not active at pre-synaptic DA₂ receptors. The results suggest that the vaso- dilator activity of fenoldopam is mediated by specific agonist activity at DA₁ receptors. In man Stote *et al.* (1983) demonstrated that fenoldopam increases *p*-aminohippurate clear- ance but does not affect inulin clearance. In their study fenoldopam had a diuretic and natriuretic effect. The changes were shown to be diminished by metoclopramide.

The present study was undertaken to assess the effect of single doses of 100 mg of fenol- dopam on effective renal plasma flow (ERPF); glomerular filtration rate (GFR); blood pres- sure (BP) and heart rate in normal individuals. Plasma renin activity (PRA) and aldosterone (PA) were also measured because of the reports that stimulation of dopamine receptors can influence the renin/angiotensin/aldosterone system (Imbs *et al.*, 1975. Campbell *et al.*, 1981).

Methods

The subjects were seven healthy male volun- teers, mean ($\pm$ s.e. mean) age 30.6 ($\pm$ 1.6) years, mean weight 72.9 ($\pm$ 2.6) kg. All gave informed consent; the ethical committee of the General Infirmary at Leeds had given its approval to the experimental protocol.

Each subject was studied on 2 days separ- ated by at least 1 week; receiving fenoldopam on 1 day and placebo on the other, according to a randomised double-blind protocol. On study days subjects were asked to take a light break- fast low in salt; xanthine containing drinks (tea, coffee, cocoa, cola) were to be avoided for 12 h; and alcohol for 24 h before the study. At 09.20 h intravenous cannulae were inserted: one into an ante-cubital fossa vein of each arm. The subjects remained seated during the period of the experiment from 09.30 h to 15.30 h except when passing urine. Fenoldopam (or placebo) was taken at 11.30 h (0 h) with the preceding 2 h constituting a run-in period during which base- line measurements were made (Figure 2). The pulse rate and BP were measured in duplicate every 15 min using a Dinamap monitor (Critikon Ltd). Hydration was standardised by giving 200 ml of distilled water every hour starting at -2 h. Timed urine collections were made from -2 to 0; 0 to 2; and 2 to 4 h. Subjects were also asked to pass urine at 3.5 h for the measurements of renal clearance. Venous blood for PRA and PA was taken immediately before; and 1 and 3.5 h after drug ingestion (before rising to pass urine at 0 and 3.5 h). Venous blood was also taken for a full blood count, differential white cell count, plasma electrolytes, urea, creatinine and liver enzymes (aspartate transaminase, alanine trans- aminase, alkaline phosphatase, lactic dehydro- genase and γ -glutamyl transferase). These samples were taken at the beginning of the experiment and 24 to 48 h after each study day respectively.

Figure 1 Molecular structures of dopamine and fenoldopam

Figure 2 Protocol for the clinical studies

ERPF and GFR were measured by calculating the clearance of I^{125} orthoiodohippurate (I^{125} OIH) and Cr^{51} ethylene diamine tetraacetic acid (Cr^{51} EDTA). A bolus injection of 10 μ Ci I^{125} OIH immediately followed by 30 μ Ci Cr^{51} EDTA was given into one cannula 30 min after drug ingestion. Blood samples were taken from the opposite arm at approximately 2, 5, 10, 15, 20, 30, 45, 60, 90 and 180 min and urine collections made at 90 and 180 min. After γ counting of plasma and urine the clearance of each isotope was calculated by the cumulative integral method (Harries *et al.*, 1972). Values for ERPF and GFR were calculated over the time periods 0 to 90 and 90 to 180 min after isotope injection by dividing the amount of I^{125} OIH and Cr^{51} EDTA excreted by the area under the respective plasma concentration curves during each period. The areas under the plasma concentration curves were measured by planimetry.

Duplicate urine samples were kept at -20°C for a month to allow the isotopes to decay before analysis by the Department of Chemical Pathology for sodium and potassium content by flame photometry. PRA was assayed by incubating plasma in the presence of angiotensinase inhibitors to form angiotensin I, and the peptide then determined by radioimmunoassay (Haber *et al.*, 1969). The intra and inter assay coefficients of variation were 6.1 and 6.2% respectively. Specimens were assayed for PA in a single batch by radioimmunoassay using antibody coated tubes (Diagnostic Products Corp.) and the intra assay coefficient of variation was 6.8%.

Statistical analysis of the pulse rate and BP data was carried out by repeated measures analysis of variance using the statistical package BMPD 2V (Dixon & Brown, 1979). Friedman non-parametric analysis of variance was used to analyse the treatment and placebo groups separately. The changes in urine flow rate, sodium and potassium excretion rates, PRA

and PA were analysed by repeated measures analysis of variance with subsequent comparison of single means by the Newman-Keuls test (Winer, 1971). PRA and PA were analysed in the form of log data because of lack of homogeneity of the variance. ERPF, GFR and filtration fraction were analysed by paired Wilcoxon tests in which the mean values after fenoldopam were compared with placebo and the differences over the two time periods assessed.

Results

Fenoldopam produced unequivocal haemodynamic changes (Figure 3). There was a significant fall ($P < 0.001$) in diastolic blood pressure (DBP) which was evident 30 min after drug ingestion, maximal at 45 min and lasted until 3 to 4 h after administration of the drug. Compared with the mean DBP in the hour prior to drug ingestion, DBP fell by a maximum of 9.9 mm Hg. There was no fall in the placebo group DBP. The mean pulse rate rose ($P < 0.001$), and was maximal 45 min after the drug. The systolic blood pressure (SBP) also rose ($P < 0.001$), this rise was evident at 45 min and maximal 1 h after taking the drug. Compared with the hour prior to drug administration SBP rose by a maximum of 11.5 mm Hg.

When compared with placebo, fenoldopam increased mean ($\pm$ s.e. mean) ERPF (I^{125} OIH clearance from 30 to 120 min after oral ingestion of the drug) from 436 ± 28 to 688 ± 33 ml/min ($P < 0.01$) an increase of 57.8%; GFR increased by 8.6% from 104 ± 5 to 113 ± 5 ml/min ($P < 0.01$) over the same time period and the filtration fraction fell from 0.24 ± 0.01 to 0.16 ± 0.01 ($P < 0.01$) (Figure 4). The clearances of I^{125} OIH and Cr^{51} EDTA calculated over the period from 120–210 min after fenoldopam showed a fall back to placebo values in ERPF ($P < 0.01$) and GFR (NS) and

Figure 3 The effect of fenoldopam 100 mg (●—●) or placebo (○—○) on mean pulse rate, systolic and diastolic blood pressure. Fenoldopam or placebo was given at time 0.

a concomitant rise in filtration fraction ($P < 0.01$). This trend seems clear despite possible inaccuracies in calculating the clearance of $I^{125}OIH$ over the latter period due to the small area under the plasma concentration curve.

The urine flow rate showed no significant change throughout the experiment in either group (Figure 5). Apart from the small amounts of sodium chloride, when the cannulae were flushed with heparinised saline the subjects received no sodium or potassium, over the course of the experiment. As a result the mean urinary excretion rate of sodium showed the expected fall in the placebo group. In the group who received fenoldopam the sodium excretion rate showed a small rise although this was not statistically significant (Figure 5). Fenoldopam had no significant effect on the mean urinary potassium excretion rate (Figure 5).

Analysis of variance showed significant overall differences in PRA ($P < 0.001$) and aldosterone ($P < 0.001$). In the fenoldopam treated group PRA rose from $2.2 (\pm 0.3)$ to $6.6 (\pm 1.2)$ ng AI h⁻¹ ml⁻¹ 1 h after drug ingestion ($P < 0.001$, Newman Keuls) but had returned to baseline values by 3.5 h (Figure 6). The PA concentration was slightly higher in the active treatment group at the end of the run-in period ($P < 0.05$, Newman-Keuls). At 1 h after drug administration PA in the placebo group had fallen whereas this fall was delayed after fenoldopam (Figure 6). The difference between

Figure 4 The effect of fenoldopam 100 mg (▨) vs placebo (□) on effective renal plasma flow (ERPF), glomerular filtration rate (GFR) and filtration fraction, calculated over 0.5 to 2 h and 2 to 3.5 h after drug ingestion. The histogram represents the mean, with the bars denoting the s.e. mean.

Figure 5 The effect of fenoldopam 100 mg (▨) vs placebo (□) on urine flow rate, sodium and potassium excretion rates. Fenoldopam or placebo was given at time 0. The histogram represents the mean; with the bars denoting the s.e. mean.

Figure 6 The effect of fenoldopam 100 mg (●—●) vs placebo (○—○) on plasma renin activity and plasma aldosterone. Fenoldopam or placebo was given at time 0. The data is expressed as the mean with bars denoting the s.e. mean.

drug and placebo at 1 h was significant ($P < 0.001$, Newman-Keuls).

There were no serious adverse reactions. Three subjects experienced a sensation of facial flushing and palpitation which lasted up to 30 min and occurred within the first hour after administration of fenoldopam. There were no changes in the blood counts, liver function tests or other safety parameters monitored.

Discussion

The BP measurements show a pronounced fall in DBP. The increased pulse rate and SBP are probably the result of reflex stimulation of the sympathetic nervous system since fenoldopam has no direct effect on heart muscle when studied *in vitro* (Hahn *et al.*, 1982). Although dopamine at low doses is a renal vasodilator it is generally held to have little effect on heart rate and BP in man (McDonald *et al.*, 1964). However, Eble (1964) demonstrated in anaesthetised dogs that even low doses which are

vasodilator in the kidney produce α -adrenoceptor mediated vasoconstriction in the femoral and carotid circulations. After pretreatment with phenoxybenzamine, dopamine lowers BP (Goldberg, 1972) indicating that a more specific dopamine receptor agonist such as fenoldopam, without α -adrenoceptor agonist activity would be expected to have a vasodepressor effect. Fenoldopam is considerably more potent than dopamine at the renal vascular dopamine receptor (Ackerman *et al.*, 1983). Studies published to date give no indication that fenoldopam produces non-specific vasodilatation. Ackerman *et al.* (1982) showed in anaesthetised dogs that fenoldopam increased renal blood flow but in contrast had very little effect on blood flow in the iliac artery. In a subsequent paper Ackerman *et al.* (1983) compared fenoldopam with nitroprusside in a perfused hind limb preparation and found that nitroprusside actively decreased perfusion pressure whereas fenoldopam was inactive. The facial flushing experienced by three of our subjects (and reported by Stote *et al.*, 1983) suggests that cutaneous vasodilatation

does occur. There is evidence for dopamine receptors in the cutaneous circulation, at least in the dog (Lang *et al.*, 1976), and these may mediate this phenomenon. Further experiments are needed in which peripheral blood flow is measured by plethysmography or Doppler methods.

The results showed a pronounced renal vasodilator effect which is of a similar order to that produced by dopamine (McDonald *et al.*, 1964). Such a large rise in ERPF and fall in filtration fraction implies an effect on both the afferent and efferent arterioles but since GFR also increased there would appear to be a greater vasodilator effect at the afferent arteriole. A direct effect on glomerular capillary tone or permeability cannot be excluded. Nerve endings thought to release dopamine have been identified in the glomerular tuft (Dinerstein *et al.*, 1979; Bell *et al.*, 1978) and are likely to be the prejunctional counterpart of dopamine receptors which mediate renal arteriolar vasodilatation. The effect of fenoldopam, a specific DA₁ receptor agonist demonstrates that dopaminergic influences can profoundly increase glomerular blood flow.

The small increase in the mean urine sodium excretion rate after fenoldopam is of interest although it was not significantly different statistically from the fall after placebo. Further studies with more rigorous pre-study control of sodium intake might demonstrate a more definite effect since Stote *et al.* (1983) did show a significant diuretic and natriuretic response to fenoldopam, although their study was not double-blind or placebo controlled. When compared with the work of McDonald *et al.* (1964) it appears that fenoldopam has considerably less natriuretic effect than dopamine. The effect of fenoldopam on PRA (see below) would seem likely to counteract any increased tendency to sodium excretion due to an increased GFR or as a result of a direct effect of fenoldopam on tubular dopamine receptors. The urine flow rate and the urinary potassium excretion rate showed no significant change after fenoldopam when compared with placebo. Dopamine infusion in normal man has been shown to have little effect on the excretion rate of potassium (McDonald *et al.*, 1964).

The plasma renin activity increased significantly 1 h after drug ingestion in a manner

similar to the response produced by other vasodilators such as hydralazine (Ueda *et al.*, 1970) or minoxidil (Brunner *et al.*, 1978). It has been suggested that there are receptors for dopamine on the JG cells which depress renin output (Sowers *et al.*, 1981) but the drop in blood pressure in our experiments appears to be the overriding stimulus to renin secretion after fenoldopam. It has been shown that propranolol greatly reduces this rise in PRA (Brennan *et al.*, 1983) suggesting that it is mediated via the baroreceptors and sympathetic nervous system. Although PA at 1 h in the fenoldopam treated group was significantly greater than in the control group the PA concentration did not show a rise similar to the increase in PRA suggesting that fenoldopam may have an independent effect inhibiting aldosterone secretion from the adrenal gland. This could result from agonist activity by fenoldopam at receptors for dopamine in the zona glomerulosa (Noth *et al.*, 1980).

In summary fenoldopam is the first specific peripheral DA₁ receptor agonist to become available. It lowers diastolic blood pressure and has a novel pharmacological profile which differentiates it both from other vasodilators and from other dopamine agonists such as bromocriptine. It seems likely to be effective in hypertension and congestive heart failure with perhaps less tendency to produce sodium retention than known vasodilators. Our group has produced evidence that renal dopamine mobilization on salt loading is deficient both in essential hypertension (Perkins *et al.*, 1980; Harvey *et al.*, 1984) and in chronic renal failure (Casson *et al.*, 1983). Treatment with a peripheral dopamine receptor agonist may be particularly appropriate in both these clinical conditions.

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