Effects of fenoldopam, a specific dopamine receptor agonist, on blood pressure and left ventricular function in systemic hypertension

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1 The effects of fenoldopam, an orally active, specific dopamine- $_1$ receptor agonist, were studied in eleven patients with essential hypertension, using intra-arterial blood pressure recording and equilibrium gated radionuclide angiography.

2 A single dose of fenoldopam 100 mg produced a fall in blood pressure (BP) starting after 20 min. The maximum BP reduction (23/25 mm Hg) occurred after 50 min and was accompanied by a heart rate (HR) increase of 10 beats min^{-1} . The acute effects on BP lasted for 130 min.

3 After 8 weeks of fenoldopam 100 mg, twice daily, only a small, statistically insignificant, hypotensive effect was still apparent after each dose of drug. The duration of the effect was too short to be clinically useful. Tilt-testing produced a BP fall of 24/14 mm Hg and a HR increase of 17 beats min^{-1} . Three patients experienced symptoms of postural hypotension during the study.

4 The drug attenuated the blood pressure rise produced by dynamic cycle exercise and isometric hand grip.

5 Acute administration of fenoldopam increased the left ventricular ejection fraction from 61% to 71% ($P < 0.005$) and increased the peak filling rate from 2.52 to 3.86 end diastolic vol s^{-1} ($P < 0.002$). After chronic fenoldopam administration, the left ventricular ejection fraction was 65% ($P = \text{NS}$) pre-dose, rising to 69% ($P < 0.02$) post-dose and the peak filling rate was increased from 2.7 to 3.38 end diastolic vol s^{-1} ($P < 0.01$) 60 min post-dose. There was also a significant increase of the first one-third filling fraction from 0.24 to 0.47 ($P < 0.01$) pre-dose, indicating improved diastolic function.

6 Although the duration of action of this formulation of fenoldopam is too short to recommend it for clinical use, a slow-release preparation would merit further investigation for treatment of hypertension and heart failure.

Keywords fenoldopam intra-arterial blood pressure left ventricular function

Introduction

In essential hypertension renal arteriolar constriction often occurs, resulting in increased renal vascular resistance and diminished renal plasma

flow (Reeve *et al.*, 1978). These abnormalities can be reversed by administration of small doses of dopamine, which stimulates specific receptors

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in the renal vasculature and lowers systemic arterial blood pressure (Schmidt *et al.*, 1985; Ackerman *et al.*, 1983). However, dopamine lacks specificity, so that higher doses increase systemic blood pressure through stimulation of α -adrenoreceptors, while even higher doses increase the rate and contractile force of the heart through stimulation of β -adrenoreceptors (Hahn *et al.*, 1982).

The identification of two dopamine receptor subtypes, DA₁ and DA₂, has been aided by the development of specific agonists. One such compound, fenoldopam (SK + F 82526-J), is a potent selective DA₁ agonist, which does not stimulate adrenoreceptors. Preliminary studies in hypertensive subjects have shown useful reductions of blood pressure maintained for up to 3 weeks, associated with increased renal plasma flow, a fall in renal vascular resistance, and natriuresis (Ventura *et al.*, 1984; Carey *et al.*, 1984). This drug is a novel compound, which has also been reported to improve systolic function in hypertension (Ventura *et al.*, 1984) and in congestive heart failure (Young *et al.*, 1985). It is possible that the diastolic abnormalities observed in patients with hypertension by radionuclide ventriculography (Inouye *et al.*, 1984) could also be improved by this drug.

This present study was therefore designed to examine the magnitude and duration of blood pressure reduction produced by fenoldopam, using intra-arterial blood pressure recording, and to evaluate the effect of the drug on left ventricular systolic and diastolic function in patients with essential hypertension, using gated radionuclide angiography.

Methods

The study was conducted according to a protocol approved by the Hospital Ethical Committee.

Five men and six women, mean age 49 years (range 35–60) were recruited from the Northwick Park Hospital Hypertension Clinic. All had essential hypertension, defined as a diastolic blood pressure of more than 95 mm Hg after at least 2 weeks free of treatment, and all gave their informed, written consent to participation in the study.

Blood pressure measurement

Intra-arterial blood pressure recording was carried out as described previously (Millar-Craig *et al.*, 1978). On the first day of the recording, after insertion of the intra-arterial cannula and calibration of the equipment, the patients under-

went a 20 min period of supine rest, followed by passive tilting to 60° for 5 min. Isometric exercise at 50% of maximum voluntary hand-grip for 2 min was followed by maximum symptom-limited cycle exercise in 3 min stages at workloads of 250, 400, 700 and 1000 kpm min⁻¹. The patients left the hospital wearing the recording equipment and were encouraged to continue their normal daily activities, returning for equipment checks and calibration in the evening. On the following morning, 100 mg of fenoldopam was administered orally and the intra-arterial blood pressure recording was continued for a further 2 h before the equipment was removed.

Radionuclide angiography

On the second morning of the intra-arterial blood pressure recording the patients were injected with stannous pyrophosphate, followed 20 min later by 740 MBq of technetium-99m, to label the red cells. A 32 frame, ECG-gated equilibrium blood pool scan was recorded using an Elscint Apex 215M digital gamma camera. The ECG gating tolerance was set at 5% to exclude extrasystolic beats, post extrasystolic beats and the effects of sinus arrhythmia. Five million counts were recorded in the left anterior oblique position with a caudal tilt to produce the best separation of the ventricles. Repeated acquisitions were obtained 40, 80 and 120 min after acute administration of 100 mg fenoldopam orally.

The data from each acquisition was subjected to 9-point smoothing and a continuous loop cine-angiogram was examined for wall motion abnormalities. A semi-automatic, second derivative, edge detection programme was used to define the left ventricular region of interest. After subtraction of a background region, a high resolution time-activity curve was constructed. The 32 frames and the 5% ECG gating tolerance ensured that the diastolic portion of the time-activity curve was well preserved, allowing the following variables to be calculated: ejection fraction (stroke counts/end diastolic counts), ejection rate, time to peak filling (time from end systole to the point of maximum filling), peak filling rate (measured over 100 ms at the steepest portion of the filling curve), first one-third filling fraction (obtained by dividing diastolic time into three parts and dividing stroke counts over the first third of diastole by total stroke counts). This latter figure was normalised to cycle length. The methods used to calculate the diastolic filling measurements have been described in detail previously (Inouye *et al.*, 1984).

The patients then took a fixed dose of fenoldopam 100 mg twice daily, before meals, for the

next 8 weeks and then the intra-arterial blood pressure recording and radionuclide angiography were repeated. On the first morning of the second intra-arterial blood pressure recording, the dose of fenoldopam was administered 1 h before the exercise testing, which followed the same protocol used at the start of the study, thus allowing assessment of the exercise blood pressure at the expected time of maximum drug effect. After the exercise test, the intra-arterial blood pressure recording was continued for 24 h. On the following morning, the gated radionuclide angiogram was recorded before, and 60 min after, the morning dose of fenoldopam.

Routine biochemistry and haematology results were recorded at the start and finish of the study. The patients were reviewed at fortnightly intervals, to ensure that their blood pressure did not rise to unacceptable levels, and enquiry was made for side effects at each visit.

The results were analysed using Student's paired *t*-test (two-tailed).

Results

Blood pressure

Eleven patients entered the study and completed the first period of intra-arterial blood pressure recording. Nine patients completed the second intra-arterial recording, two patients having withdrawn because of side effects. The initial blood pressure recording of one patient was lost due to disconnection of the infusion tubing from the intra-arterial cannula.

The first 100 mg dose of fenoldopam produced a perceptible reduction of blood pressure 20 min. after administration (Figure 1). The maximum blood pressure fall was 23/27 mm Hg after 50 min ($P < 0.002$) and this was accompanied by a heart rate increase of 10 beats min^{-1} ($P = \text{NS}$). The blood pressure reduction was no longer apparent after 130 min.

After 8 weeks of treatment, the effects of the twice daily drug administration were still discernable for 1 to 2 h, but did not achieve statistical significance, and there was no sustained blood pressure reduction (Figure 2).

Fenoldopam administration produced a reduction of the blood pressure at all times during the tilt test (Figure 3); the maximum reduction of 24/14 mm Hg occurred 75 s after the start and was accompanied by a statistically significant heart rate increase of 17 beats min^{-1} ($P < 0.05$). The lack of statistical significance of the BP changes was partially due to the small number of subjects completing the test.

Figure 1 Pooled intra-arterial blood pressure and heart rate trends in 10 subjects in the 160 min following administration of 100 mg of fenoldopam orally, compared with the same period the previous day. ● untreated day, ○ treated day. *** $P < 0.005$.

Fenoldopam reduced peak systolic blood pressure during isometric exercise by 30 mm Hg ($P < 0.05$, Figure 4). During cycle exercise, fenoldopam reduced the systolic, and to a lesser extent the diastolic, blood pressure at equivalent work loads. The maximum systolic blood pressure reduction was 28 mm Hg and the maximum diastolic blood pressure reduction was 11 mm Hg (Figure 5).

Left ventricular function

The maximum effect of the first dose of fenoldopam on left ventricular function was apparent after 40 min when there was a statistically significant increase of ejection fraction, ejection rate and peak filling rate (Table 1). The ejection fraction changes were sustained at 120 min but the other measurements showed a tendency to return to baseline values by this time.

After chronic treatment with fenoldopam, the ejection fraction and peak filling rate just before drug administration were both increased above

Figure 2 Comparison of intra-arterial blood pressure and heart rate in eight subjects before and after 8 weeks of treatment with fenoldopam 100 mg, twice daily. ● untreated, ○ treated.

the baseline values, but these measurements only achieved statistical significance 1 h after the drug administration, when the values reached levels comparable with those observed 40 min after the first dose of fenoldopam. The first one-third filling fraction was also significantly increased by chronic treatment with fenoldopam. No abnormalities of left ventricular wall motion were detected on visual examination and phase analysis of the radionuclide ventriculogram.

Adverse effects

Seven patients experienced side effects during the study; four complained of headaches, palpitations or nausea, three complained of flushing, two suffered dizziness, worse after drug ingestion, and nasal congestion and anxiety were each mentioned once. One man withdrew because of headache and flushing. One woman withdrew because of palpitations and flushing. In addition, one patient fainted following the cycle exercise accompanying the second intra-arterial recording. Recovery was immediate when the patient was laid flat. No significant changes of biochemistry or haematology values occurred during the study.

Figure 3 Blood pressure and heart rate response to passive tilting in seven patients before and after 6 weeks of treatment with fenoldopam 100 mg twice daily. ● untreated, ○ treated. *** $P < 0.005$.

Discussion

These results demonstrate that fenoldopam administered acutely to hypertensive subjects lowers intra-arterial blood pressure for approximately 2 h. The magnitude of the acute blood pressure reduction was sufficiently large to produce symptoms of postural hypotension in three patients, an observation confirmed by the intra-arterial blood pressure recording. The time course of the blood pressure reduction we observed agreed well with previous observations in normal subjects (Harvey *et al.*, 1985) and hypertensive patients (Ventura *et al.*, 1984; Carey *et al.*, 1984; Harvey *et al.*, 1986). The postural fall of blood pressure was also documented during passive tilting, when there was an accompanying reflex

Figure 4 Comparison of blood pressure and heart rate changes produced by isometric hand grip before and after 6 weeks of treatment with fenoldopam 100 mg twice daily. The reduction of systolic BP marked * was significant at $P < 0.05$ level: □ untreated, ■ treated.

tachycardia; also, during chronic drug administration, palpitations featured prominently amongst the side effects.

After administration of fenoldopam for 8 weeks there was no evidence of any sustained hypotensive effect due to the drug, although each drug produced a short lived effect of similar duration to the acute effect. The blood pressure increases accompanying isometric and dynamic exercise were attenuated by fenoldopam administration. If the prognosis of hypertension is more closely related to ambulatory blood pressure than resting blood pressure changes, as Sokolow has suggested (Sokolow *et al.*, 1966), then emphasis should be placed on testing new drugs for efficacy in modifying exercise induced increases in blood pressure,

Figure 5 The blood pressure and heart rate response to cycle exercise before and after 6 weeks of treatment with fenoldopam 100 mg twice daily. ● untreated, ○ treated. * $P < 0.05$.

rather than merely reporting drug effects on casual, resting blood pressure.

Fenoldopam has been shown to reduce total peripheral resistance in hypertensive patients with an accompanying increase in cardiac index, ejection fraction and ejection rate (Ventura *et al.*, 1984). The drug is not thought to have positive inotropic effects (Hahn *et al.*, 1982). However, the velocity of circumferential fibre shortening is improved in hypertensive patients (Ventura *et al.*, 1984), and favourable haemodynamic changes have also been reported in congestive heart failure (Young *et al.*, 1985). The radionuclide measurements in this study confirmed that fenoldopam increased ejection fraction and ejection rate, these effects being most apparent at the time of maximum blood

Table 1 Systolic and diastolic function measurements obtained during radionuclide angiography, before drug administration, after a single oral of fenoldopam 100 mg, and after fenoldopam 100 mg, twice daily, for 6 weeks

	Untreated	Fenoldopam 100 mg (40 min post-dose)	Treated (pre-dose)	Treated (60 min post-dose)
<i>n</i>	11	11	9	9
Ejection fraction (%)	61(9.6)	71(8.9)**	65(8.9)	69(7.1)****
Ejection rate (counts s ⁻¹)	2.0(0.4)	2.8(0.8)****	2.0(0.3)	2.6(0.5)***
Peak filling rate (end diastolic vol s ⁻¹)	2.5(0.7)	3.9(1.1)*	2.7(0.5)	3.4(0.9)***
Time to peak filling (ms)	200(56)	180(66)	167(36)	224(65)
First one third filling fraction	0.24(0.14)	0.28(0.18)	0.47(0.10)***	0.32(0.16)

The results are shown as mean (s.d.). * $P < 0.02$, ** $P < 0.01$, *** $P < 0.005$, **** $P < 0.002$.

pressure reduction. These improvements in cardiac systolic function after chronic drug administration were accompanied by an increased peak filling rate and improved first one-third filling fraction. The increase in peak filling rate could have occurred as a consequence of the increase in ejection fraction and the rise in heart rate, but the improved first one third filling fraction was more likely to represent a genuine improvement in diastolic function, as the measurement does not correlate significantly with heart rate when it is normalised to cycle length (Inouye *et al.*, 1984). Similar abnormalities of diastolic function have been observed in patients with coronary disease (Mancini *et al.*, 1983), but this was not a likely explanation for the changes observed in these patients, as they were all asymptomatic, and had normal left ventricular wall motion.

It is thought that the hypotensive effects of fenoldopam may be mediated through its renal actions. However, the side effects in this study were typical of acute arterial vasodilatation, and the direction and time course of the haemodynamic and radionuclide angiographic changes suggested that systemic arterial dilatation was the predominant mechanism of blood pressure reduction, particularly after acute administration. Harvey *et al.* (1985) and Stote *et al.* (1983) have reported facial flushing and palpitations produced by fenoldopam and they suggested that these side effects were due to arterial vasodilatation. Fenoldopam has been demonstrated to reduce

peripheral arterial resistance in the isolated dog limb by postganglionic DA₁ receptor stimulation (Lokhandwala *et al.*, 1985). A recent reviewer concluded that there is good evidence for the existence of peripheral dopamine receptors in the renal, mesenteric, cerebral, coronary, hepatic and femoral vessels (Lokhandwala & Barrett, 1982).

It has been suggested that nausea may result from stimulation of dopamine receptors in the chemoreceptor trigger zone (Lokhandwala & Barrett 1982). However, these are DA₂ receptors, and, as fenoldopam is a specific DA₁ agonist, we consider it more likely that the drug was producing nausea through gastric irritation in our patients.

In conclusion, fenoldopam lowers the arterial blood pressure acutely, but shows no evidence of any sustained hypotensive effect after twice daily administration for 8 weeks. The short duration of action makes this formulation of the drug unsuitable for routine treatment of hypertension, but a slow-release formulation of the drug might be useful in the treatment of hypertension and, because of the arterial vasodilatory properties, also in the treatment of congestive cardiac failure. Such a formulation might also reduce the incidence of side effects.

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