Arterial vasodilating profile and biological effects of pinacidil in healthy volunteers

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- 1 The effects of pinacidil (25 mg, sustained release formulation) a) on systemic (arterial pressure, cardiac output) and regional (brachial and carotid arteries' diameters and flows) haemodynamics (pulsed Doppler techniques), b) on sympathetic (plasma noradrenaline) and renin-angiotensin (plasma renin activity) systems, and c) on atrial natriuretic factor have been investigated and compared with those of a placebo during the 12 h period following oral administration in a randomized, double-blind and cross-over study performed in six healthy volunteers. Simultaneously, the plasma levels of pinacidil and of its active metabolite, pinacidil *N*-oxide, were determined.
- 2 As compared with placebo, pinacidil decreased systemic vascular resistance and arterial blood pressure but cardiac output was not modified.
- 3 Pinacidil significantly increased brachial and carotid arteries' diameters (by 7 and 8% respectively) and flows (by 60 and 17% respectively) and decreased forearm vascular resistance (by 43%). Thus, pinacidil dilates both large and small arteries, increases large vessels' compliance and redistributes blood flow towards the muscular vascular bed. These effects peaked at 4 h and their duration at the brachial level was 8 h.
- 4 Pinacidil administration resulted in a stimulation of both sympathetic (increases in heart rate and plasma noradrenaline) and renin-angiotensin systems, and induced a transient increase in atrial natriuretic factor.
- 5 The duration of pinacidil haemodynamic effects at the brachial level is consistent with the pharmacokinetic data which show that pinacidil and pinacidil *N*-oxide plasma levels almost plateaued between 3 and 8, and 2 and 8 h respectively after oral administration of the sustained release formulation used.

Keywords potassium channel openers pinacidil pulsed Doppler regional arterial blood flows healthy volunteers

Introduction

Potassium channel openers, a newly developed group of cardiovascular drugs, have been shown to exert direct vascular relaxant effects by activating plasmalemmal K^+ channels, increasing K^+ efflux from the cell and inducing membrane hyperpolarization (Cook, 1988). Hence, potassium channel openers exhibit potent vasodilating and hypotensive or antihypertensive properties but the reflexly-mediated stimulation of the sympathetic and renin-angiotensin systems can minimize their therapeutic efficacy.

In animal studies, it has been shown that the vasodilating properties of potassium channel openers do not affect homogeneously the different vascular beds, e.g. reducing preferentially coronary, gastrointestinal and cerebral vascular resistances in the rabbit (Hof *et al.*, 1988) or muscular vascular resistance in the rat (Cavero *et al.*, 1989; Richer *et al.*, 1989, 1990). In man, only one study demonstrated an increase in forearm blood flow after direct infusion of cromakalim into the brachial artery (Webb *et al.*, 1989). But it is not known whether,

besides arterioles, potassium channel openers also dilate large conductance vessels, an effect which might contribute to decrease morbidity in hypertension (Safar *et al.*, 1983). Therefore, the main goal of this study was to investigate in the healthy volunteer the systemic and regional (brachial and carotid resistance and conductance vessels) haemodynamic effects of one of these drugs, pinacidil (Arrigoni-Martelli *et al.*, 1980; Petersen *et al.*, 1978; Weston *et al.*, 1988) during a placebo-controlled, double-blind and cross-over trial. Simultaneously, the effects of pinacidil on biological markers of the sympathetic and renin-angiotensin systems as well as its pharmacokinetics were determined.

Methods

Subjects and treatments

Six healthy volunteers, aged 22–29 years, weighing 60–78 kg, took part in the investigation. All of them had given written informed consent for the study, which was approved by the Hospital Ethics Committee. Subjects were deemed healthy on the basis of a complete medical examination including normal ECG and thoracic X-ray. Subjects free from any other medication prior to and during the entire period of the trial were given orally, in a random order and under double-blind conditions, either pinacidil, 25 mg, or a placebo at a 1 week interval.

Parameters investigated

The following clinical and biological parameters were investigated before and at regular intervals after drug intake:

Systemic haemodynamics Arterial systolic (SAP) and diastolic (DAP) blood pressures and heart rate (HR) were obtained using a Roche Sentron automatic monitor (Johnson, 1989) which was positioned around the left arm of the recumbent volunteer and programmed to record these parameters every 10 min, one given value corresponding to the mean of three consecutive measurements. Mean arterial pressure (MAP) was then calculated as:

$$\text{MAP} = \text{DAP} + \frac{\text{SAP} - \text{DAP}}{3}$$

Cardiac output (CO) was measured with a pulsed Doppler system (2.25 MHz, Vingmed SD50) after echographic determination of the diameter of the aorta (Diasonics, DRF 200). Briefly, the diameter of the ascending aorta was first measured at the level of the valve leaflets on the long-axis parasternal view obtained with the bidimensional echocardiography. Then, the Doppler transducer was placed in the suprasternal notch and angulated to obtain the best Doppler signal which corresponds to the presumed direction of the blood flow in the ascending aorta. Finally, the sample volume was positioned in the ascending aorta just above the valve leaflets. Doppler signals were recorded on photographic paper, and cardiac output was automatically determined

with a computer system which integrated Doppler signals and aortic diameter (Huntsman *et al.*, 1983; Touche *et al.*, 1984). Each individual reported value corresponds to the mean of three consecutive measurements which did not differ from each other by more than 5%. For aortic diameter and cardiac output measurements, within subject variability was 1 and 3% respectively whereas between subject variability was 7 and 11% respectively. Total peripheral resistance (TPR) was calculated as the mean arterial pressure/cardiac output ratio.

Regional arterial haemodynamics Diameters and flows of the brachial and carotid arteries were measured transcutaneously using a bidimensional pulsed Doppler system (8 MHz, Echovar Doppler pulsé, Alvar Electronic) as previously described (Safar *et al.*, 1981; Thuillez *et al.*, 1984). This Doppler system, which has an ultrasonic frequency of 8 MHz, has two main original characteristics: (a) a double transducer probe that enables the incidence angle of the ultrasonic beam with the vessel axis to be known and then, after calibration, the blood velocity absolute value in the investigated artery to be measured, and (b) a range-gated time system of reception that permits the sample volume size to be chosen and moved across the arterial lumen to determine the distance between the arterial walls and the transducer, i.e. the arterial diameter. Then arterial mean blood velocity through the vessel cross-section was obtained by adjusting the electronic gate to the corresponding arterial diameter and depth. The volumic blood flows of the artery (Q) were calculated using the formula: $Q = \pi \cdot D^2 \cdot V_m / 4$, where V_m is the mean blood velocity and D the arterial diameter. All measurements were repeated three times in each patient. For brachial and carotid arteries blood flow velocities measurements, within subject variability was 5 and 4% respectively whereas between subject variability was 16 and 11%. Finally the forearm vascular resistance (FVR) was calculated as the mean arterial pressure/volumic flow ratio.

Biological parameters investigated were: plasma renin activity (PRA) (Ménard *et al.*, 1972) and plasma atrial natriuretic factor (PANF) (Lang *et al.*, 1985) measured by radioimmunoassay, and plasma noradrenaline (PNA) (Causon *et al.*, 1981) measured by high performance liquid chromatography.

Pinacidil pharmacokinetics Plasma levels of pinacidil and of its active metabolite, pinacidil N-oxide (Eilertsen *et al.*, 1982) were measured by reversed phase h.p.l.c. using automated solid phase extraction/injection after addition of N-cyano-N'-(1-ethyl-1-methylpropyl)-N''-4-pyridil guanidine N-oxide as internal standard. Column was a Lichrospher RP 18 Select B, 7 μ m, 125 $\times$ 4 mm (Merck, Lichrocart h.p.l.c. cartridge) column, mobile phase was: acetonitrile-0.02 M phosphate buffer pH = 2.5 17–83 v:v, and flow rate was 2.5 ml min⁻¹. The detector was an u.v. Merck-Hitachi 655A detector, wave length: 285 nm. Retention times were 2.5, 4 and 6 min for pinacidil, pinacidil N-oxide and the internal standard respectively. Sensitivity of the method was 3 ng ml⁻¹ for pinacidil and 5 ng ml⁻¹ for pinacidil N-oxide. Coefficient of variation of the assay method was 6% for pinacidil and 7% for pinacidil N-oxide.

Experimental protocol

After overnight fasting and after a light breakfast without tea, coffee (or alcoholic beverage) taken at 07.00 h, each volunteer arrived at the laboratory at 07.30 h. A catheter was immediately inserted into a right forearm vein, the automatic blood pressure and HR monitor was positioned around the contralateral arm and the subject rested in the supine position.

At 08.30 h, the basal clinical parameters: SAP, DAP, HR, carotid artery blood flow (CBF) and diameter (CAD), brachial artery blood flow (BBF) and diameter (BAD) and cardiac output were measured. Blood samples for determination of PRA, PANF, PNA and for pharmacokinetics were collected.

At 09.00 h, the volunteer was given his treatment orally together with 100 ml of water.

SAP, DAP, HR were automatically recorded every 10 min over a 12 h period following drug administration while other clinical parameters were determined at 2, 4 and 8 h. Blood sampling for determination of PRA, PANF and PNA was performed at 2, 4, 8 and 10 h and blood sampling for pharmacokinetics at 1, 2, 3, 4, 6, 8, 10 and 12 h.

The volunteer remained in the supine position and no tea, coffee, alcoholic beverages or smoking was allowed during the 12 h duration of the experiment. Finally, the volunteer was asked at regular intervals to fill out a questionnaire as to his general tolerance to the drug.

Drug

Pinacidil was used as its 25 mg sustained release capsules formulation (Pindac®).

Statistical analysis

Results shown are means $\pm$ s.e. mean.

For each parameter a) mean basal values measured or calculated before each drug administration were compared by means of a Student's paired *t*-test, and b) statistical analysis of the data obtained at different time intervals after administration of the two treatments was performed on the differences (in absolute values) *vs*

predrug values using a three way analysis of variance followed by a Newman-Keuls test.

Results

Table 1 indicates the mean basal values calculated for each clinical and biological investigated parameter before pinacidil or placebo administrations. For none of these parameters was there a significant difference between its two mean basal values.

Systemic haemodynamics

Figures 1 and 2 illustrate the kinetics of the variations of SAP, DAP, MAP, HR, CO and TPR induced by the two treatments.

As compared with placebo, pinacidil significantly ($P < 0.05$) decreased SAP from 3 to 6 h (with a -9% peak effect at 4 h) and DAP from 2 to 8 h (with a -14% peak effect at 2–3 h) and increased HR with a maximal effect ($+7\%$ *vs* -6% after placebo) at 2 h after drug administration (Figure 1). Pinacidil also significantly decreased total peripheral resistance ($P < 0.01$) by -14 , -8 and -4% (*vs* $+9$, $+16$ and $+20\%$ after placebo) at 2, 4 and 8 h, and slightly but not significantly increased cardiac output (Figure 2).

Regional haemodynamics

Figure 3 illustrates the kinetics of the variations of BBF, BAD and FVR induced by the two treatments. As compared with placebo, pinacidil significantly increased BBF ($P < 0.05$, peak effect: $+60\%$ at 4 h) and BAD ($P < 0.01$, maximal increase: $+7\%$ plateauing between 2 and 4 h) and decreased FVR ($P < 0.05$, peak effect: -43% at 4 h). As compared with its pre-drug value, the BBF/CO ratio determined 4 h after drug intake was increased by 68 ± 11 and $17 \pm 5\%$ after pinacidil and placebo respectively, the difference being significant ($P < 0.05$).

Figure 4 illustrates the kinetics of the variations of CBF and CAD induced by the two treatments. As compared with placebo, pinacidil significantly increased

Table 1 Mean basal values of all investigated parameters before treatment administration. Values are expressed as mean $\pm$ s.e. mean

	Placebo	Pinacidil
Systolic arterial pressure (mm Hg)	116.0 $\pm$ 3.2	119.0 $\pm$ 4.7
Diastolic arterial pressure (mm Hg)	62.8 $\pm$ 1.9	64.5 $\pm$ 2.4
Mean arterial pressure (mm Hg)	80.6 $\pm$ 2.1	82.7 $\pm$ 2.9
Heart rate (beats min ⁻¹)	60.7 $\pm$ 2.8	63.2 $\pm$ 4.6
Cardiac output (l min ⁻¹)	5.1 $\pm$ 0.3	5.3 $\pm$ 0.4
Total peripheral resistance (dyn s cm ⁻⁵)	1284 $\pm$ 71	1281 $\pm$ 76
Brachial blood flow (ml min ⁻¹)	75.7 $\pm$ 4.8	77.7 $\pm$ 4.3
Brachial artery diameter (mm)	4.51 $\pm$ 0.07	4.57 $\pm$ 0.06
Forearm vascular resistance (mm Hg s ml ⁻¹)	65.6 $\pm$ 5.6	64.9 $\pm$ 4.3
Carotid blood flow (ml min ⁻¹)	342.7 $\pm$ 13.8	345.5 $\pm$ 15.1
Carotid artery diameter (mm)	5.33 $\pm$ 0.16	5.17 $\pm$ 0.16
Plasma renin activity (ng l ⁻¹ min ⁻¹)	17.2 $\pm$ 1.4	20.5 $\pm$ 1.9
Plasma noradrenaline (pg ml ⁻¹)	198 $\pm$ 28	192 $\pm$ 25
Plasma atrial natriuretic factor (pg ml ⁻¹)	22.9 $\pm$ 1.4	24.2 $\pm$ 2.0

Figure 1 Kinetics of the variations (vs pretreatment values) of systolic, diastolic and mean arterial pressures (mm Hg) and heart rate (beats min^{-1}) induced by pinacidil (●) and placebo (■) during the 12 h period following oral administration. Vertical lines show the s.e. mean, with a significant difference between pinacidil and placebo shown as *, P at least < 0.05 .

CBF ($P < 0.01$) at 2 (+8%) and 4 h (+17%) and CAD ($P < 0.05$) from 2 to 8 h (peak effect: +8% at 4 h). As compared with its predrug value, the CBF/CO ratio determined 4 h after drug intake was increased by 20 ± 6 and $16 \pm 4\%$ after pinacidil and placebo respectively (NS).

Biological parameters

Figure 5 illustrates the kinetics of the variations of plasma noradrenaline, renin activity and atrial natriuretic factor induced by the two treatments.

Pinacidil long-lastingly increased plasma noradrenaline but the variations (+57, +50 and +42% at 2, 4 and 8 h respectively) were just below statistical significance ($P = 0.061$). Pinacidil significantly increased plasma renin activity at 2 (+125%, $P < 0.01$) and 4 h (+82%, $P < 0.01$) and slightly and transiently increased plasma atrial natriuretic factor at 2 h (+11%, $P < 0.05$).

Pinacidil pharmacokinetics

Figure 6 illustrates the kinetics of pinacidil and pinacidil-*N*-oxide mean plasma levels during the 12 h period following drug intake. As can be seen, pinacidil plasma concentrations peaked at 2 h and then plateaued from 3 to 8 h (between 40 and 50 ng ml^{-1}) whereas pinacidil-*N*-

Figure 2 Kinetics of the variations (vs pretreatment values) of cardiac output (l min^{-1}) and total peripheral resistance (dyn s cm^{-5}) induced by pinacidil (●) and placebo (■) during the 8 h period following oral administration. Vertical lines show the s.e. mean, with a significant difference between pinacidil and placebo shown as *, P at least < 0.05 .

oxide plasma concentrations plateaued from 2 to 8 h (between 36 and 39 ng ml^{-1}) after drug administration.

General tolerability

No serious untoward effects were encountered during this study. Headaches, related to the vasodilating effect of pinacidil were reported by three subjects. Among these three subjects, two also complained of asthenia and one of nausea and dryness of the mouth. All these side-effects appeared 2 h after drug intake and lasted 6 to 7 h.

Discussion

Pinacidil is a potassium channel opener which has been shown to be an effective antihypertensive drug in man (Kardel *et al.*, 1981; Ramsay & Freestone, 1983). This is due to the drug's potent vasodilating properties. The present study performed in healthy volunteers demonstrates that these vasodilating properties are not homogeneously distributed, affecting preferentially the muscular vascular bed and inducing at this level a favourable redistribution of blood flow. Furthermore, this study shows that pinacidil-induced vasodilation affects both small and large arteries and leads in normotensive

Figure 3 Kinetics of the variations (vs pretreatment values) of brachial blood flow (ml min^{-1}), brachial artery diameter (mm) and forearm vascular resistance (mm Hg s ml^{-1}) induced by pinacidil (●) and placebo (■) during the 8 h period following oral administration. Vertical lines show the s.e. mean, with a significant difference between pinacidil and placebo shown as *, P at least < 0.05 .

Figure 4 Kinetics of the variations (vs pretreatment values) of carotid blood flow (ml min^{-1}) and carotid artery diameter (mm) induced by pinacidil (●) and placebo (■) during the 8 h period following oral administration. Vertical lines show the s.e. mean, with a significant difference between pinacidil and placebo shown as *, P at least < 0.05 .

Figure 5 Kinetics of the variations (vs pretreatment values) of plasma noradrenaline (pg ml^{-1}), plasma renin activity ($\text{ng l}^{-1} \text{min}^{-1}$) and plasma atrial natriuretic factor (pg ml^{-1}) induced by pinacidil (●) and placebo (■) during the 10 h period following oral administration. Vertical lines show the s.e. mean, with a significant difference between pinacidil and placebo shown as *, P at least < 0.05 .

Figure 6 Kinetics of pinacidil (●) and pinacidil N-oxide (■) mean plasma levels measured during the 12 h period following oral administration of pinacidil 25 mg. Vertical lines show the s.e. mean.

subjects to a slight decrease in blood pressure and to a stimulation of the renin-angiotensin and sympathetic systems.

The potent vasodilating properties of pinacidil are clearly demonstrated by the strong reduction observed in total peripheral and forearm vascular resistances. Inasmuch as cardiac output was not simultaneously modified, this reduction resulted in a decrease in systolic and diastolic arterial pressures. Such a decrease is rather unusual in healthy volunteers with arterial vasodilators. Thus, angiotensin converting enzyme inhibitors (ACEIs) which only slightly reduce systemic vascular resistance and do not affect cardiac output (Fouad *et al.*, 1984) and phenyldihydropyridine calcium antagonists which decrease systemic vascular resistance but reflexly increase cardiac output (Thuillez *et al.*, 1989) do not affect blood pressure in normotensive subjects. However, in this study and in contrast to the data reported by Nicholls *et al.* (1986) after intravenous administration, the strong reduction in systemic vascular resistance induced by oral pinacidil was not counteracted by a simultaneous increase in cardiac output which was only maintained at its pre-drug value and hence arterial pressure decreased. In the study performed by Nicholls *et al.* (1986) in patients with suspected ischaemic heart disease, cardiac output was significantly increased by pinacidil, 0.2 mg kg⁻¹ intravenously. In the present study, cardiac output was not significantly increased but there is no real discrepancy between the two sets of data inasmuch as a) cardiac output was in our study 15% greater after pinacidil than after placebo throughout the experimental period, b) the dose of pinacidil (0.2 mg kg⁻¹ intravenously) administered by Nicholls *et al.* (1986) was greater than that we gave (25 mg, orally), and c) this 25 mg oral dose was administered as a sustained release formulation.

Regarding the mechanism of the induced vasodilation, our data show that pinacidil dilates both small and large arteries since there were simultaneously a decrease in regional vascular resistances and an increase in brachial and carotid arterial diameters. This vasodilating profile is similar to those of phenyldihydropyridine calcium antagonists like nicardipine and nifedipine (Thuillez *et al.*, 1984, 1989) and of ACEIs like perindopril (Richer *et al.*, 1987) and ramipril (Thuillez *et al.*, 1987b) but contrasts with those of verapamil (Thuillez *et al.*, 1987a) and dihydralazine (Simon *et al.*, 1983) which only dilate arterioles. Whether the increase in large conductance vessels' diameter observed with pinacidil is a direct effect of the drug or whether it is mediated through the simultaneously occurring increase in flow (shear stress) remains undetermined and further studies, including interruption of brachial flow, are necessary to answer the question. But, whichever its mechanism, the pinacidil-induced dilation of large conductance vessels is accompanied by a decrease in blood pressure, indicating an increase in arterial compliance. Hence arterial buffer function is improved, a factor which has been postulated to reduce cardiovascular morbidity in hypertension (Safar *et al.*, 1983).

Comparison of the regional haemodynamic effects of pinacidil shows that the forearm vascular bed is prefer-

entially dilated as compared with the carotid one. Thus, brachial blood flow was increased to a much larger extent (+60 vs +17%) and more long-lastingly than carotid blood flow. A similar preferential vasodilating effect in muscular vascular bed, i.e. in resistance vessels, has previously been observed in man under identical experimental conditions with other antihypertensive drugs like calcium antagonists (Thuillez *et al.*, 1984) and ACEIs (Richer *et al.*, 1987) and in animals with other potassium channel openers (Richer *et al.*, 1989, 1990). This preferential vasodilating effect of pinacidil in resistance vessels, which develops despite the simultaneous increase in sympathetic tone (evidenced by the rise in plasma noradrenaline levels), plays a major role in the drug's antihypertensive properties. Furthermore, it results in a favourable redistribution of cardiac output towards the muscular vascular bed (increase in BBF/CO ratio).

Regarding the biological data, it appears that pinacidil induces a strong stimulation of the renin-angiotensin system and a transient increase in plasma atrial natriuretic factor (ANF). The stimulation of the renin-angiotensin system, evidenced by the increase in PRA, is due both to a direct hyperpolarizing effect of pinacidil on macula densa cells (Ferrier *et al.*, 1989) and to the drug-induced reflex activation of the sympathetic system. Although responsible on the long term for some of the drug's side-effects, e.g. sodium retention, this stimulation of the renin-angiotensin system and the ensuing hyperaldosteronism cannot be considered as being involved in the early and transient increase in ANF observed during this acute study. More likely, this increase in ANF is related to pinacidil transient and reflexly mediated positive chronotropic and inotropic effects, which are known to increase ANF secretion (Payen *et al.*, 1987). Furthermore, the latter increase is apparently not counteracted by opposing factors such as a decrease in preload and in this respect, it can be pointed out that another potassium channel opener, cromakalim, has been shown to be devoid of venous dilating properties in man (Webb *et al.*, 1989).

Finally, our pharmacokinetic data show that pinacidil plasma levels exhibit two peaks (2 and 6 h) corresponding respectively to gastric and intestinal absorption of the sustained release formulation used. They also indicate that this formulation ensures almost stable plasma levels for both pinacidil and its active metabolite, pinacidil *N*-oxide, between 3 and 8, and 2 and 8 h after drug administration. Furthermore, it appears that these plasma levels are pharmacologically active since brachial haemodynamic parameters were strongly increased during the 8 h following drug intake and since all drug-induced and vasodilation-related side-effects occurred during the same period.

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