Effects of an angiotensin converting enzyme inhibitor, ramipril, on intracranial circulation in healthy volunteers

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- 1 The effects of a single oral dose (10 mg) of ramipril on (a) systemic haemodynamics (arterial pressure, cardiac output), (b) carotid artery haemodynamics (blood flow and diameter, pulsed Doppler technique), (c) intracranial haemodynamics (middle cerebral artery mean blood velocity, transcranial Doppler technique), and (d) renin-angiotensin system (plasma converting enzyme and renin activities) have been investigated and compared with those of a placebo during the 24 h period following administration in a randomized, double-blind and cross-over study performed in six healthy volunteers.
- 2 Ramipril induced a strong and sustained inhibition of plasma converting enzyme activity (−96% at 4 h, −63% at 24 h) and an increase in plasma renin activity (+993% at 8 h).
- 3 As compared with placebo, ramipril did not significantly affect arterial blood pressure, heart rate, cardiac output and total peripheral resistance.
- 4 Ramipril significantly increased carotid blood flow (by 27% at 8 h) without significantly changing carotid artery diameter, indicating, given the unchanged arterial pressure, an arteriolar vasodilation in the carotid territory.
- 5 The middle cerebral artery mean blood flow velocity underwent spontaneous modifications during the placebo period but these changes were not affected by ramipril. This lack of influence of ramipril on intracranial haemodynamics suggests that the drug-induced arteriolar vasodilation and increase in carotid blood flow only concern the extracranial, musculo-cutaneous part of the carotid territory.

Keywords ramipril angiotensin I-converting enzyme inhibitor
cerebral haemodynamics transcranial Doppler healthy volunteers

Introduction

In healthy volunteers as well as in patients suffering from hypertension or from congestive heart failure, angiotensin I-converting enzyme inhibitors (ACEIs) have been reported to lower regional vascular resistances and to increase regional blood flows of peripheral arteries (Richer *et al.*, 1987; Safar *et al.*, 1986; Simon *et al.*, 1988; Thuillez *et al.*, 1987). These properties have been demonstrated using the pulsed Doppler technique in the common carotid artery (CCA), brachial artery, and femoral artery vascular beds.

ACEI-induced changes in CCA haemodynamics are characterized in healthy volunteers by (a) an increase in carotid blood flow (CCABF) which, given the unchanged blood pressure value, indicates arteriolar vasodilation, and (b) a slight increase in CCA diameter (CCAD) which usually does not reach statistical significance

(Giudicelli *et al.*, 1991; Richer *et al.*, 1987; Thuillez *et al.*, 1987, 1991a). However, inasmuch as the CCA divides into (a) an extracranial branch which supplies muscular and cutaneous territories and (b) an intracranial branch which is a major contributor to cerebral blood flow, it was important to determine whether or not the latter benefits from ACEI-induced increase in CCABF. A few studies have addressed this question and tend to demonstrate that, probably because of cerebral blood flow autoregulation, ACEIs do not affect this parameter. This has been observed both in healthy volunteers (Schmidt *et al.*, 1990; Waldemar *et al.*, 1989) and in hypertensive patients (Frei & Muller-Brand, 1986; Minematsu *et al.*, 1987; Waldemar *et al.*, 1989) after acute or chronic administration of captopril and enalapril. However these data have been obtained by invasive

(oxygen arterio-venous difference) or radioactive (^{133}Xe dynamic single-photon-emission-computerized-tomography, SPECT) techniques which do not easily allow repeated measurements and hence the assessment of the kinetics of drugs' effects on cerebral blood flow. Moreover, in none of these studies was CCABF and cerebral blood flow simultaneously measured.

The newly developed non-invasive transcranial Doppler technique (TCD) allows instantaneous measurements of intracranial blood flow velocities (Kirkham *et al.*, 1986), especially in the middle cerebral artery (MCA). Furthermore, it has been demonstrated in man that the variations of MCA blood flow velocity at rest are correlated to those of cerebral blood flow in both hemispheres (Piepgras *et al.*, 1990) and can thus be used for repeated measurements in clinical studies (Kontos, 1989).

Ramipril is an ACEI that has already been shown to increase CCABF strongly in healthy volunteers (Thuillez *et al.*, 1987) but nothing is known about its action on cerebral blood flow. Therefore the present study was designed to investigate the effects of the drug simultaneously on CCABF and MCA blood flow velocity and to compare them over a 24 h period with those of a placebo during a double-blind and cross-over study performed in six healthy subjects, the main goal being to determine whether ramipril-induced increase in CCABF has repercussions on cerebral blood flow or not. CCABF and MCA blood flow velocity were assessed by the bidimensional pulsed Doppler and TCD techniques, respectively.

Methods

Subjects and treatments

The trial was conducted in six male healthy volunteers, aged 19 to 25 years and weighing 64 to 76 kg. All of them gave 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 electrocardiogram, normal blood pressure, and normal biological tests. The subjects, on a normal sodium diet (100 to 120 mmol Na^+ day $^{-1}$) and free of any other medication 2 weeks before and during the entire period of the trial, were given orally, in a random order and under double-blind conditions, either ramipril, 10 mg, or a placebo at a 2 week interval.

Parameters investigated

The following clinical and biological parameters were recorded before, and at regular intervals over a 24 h period after drug intake.

Systemic haemodynamics Arterial blood pressure (systolic (SAP), diastolic (DAP), and mean (MAP)) and heart rate: SAP and DAP were obtained using a Roche Sentron automatic monitor (Johnson, 1989) positioned at 07.00 h around the right arm of the recumbent volunteers and programmed to record these parameters every 10 min. One given value corresponds to the mean of

three consecutive measurements. MAP was calculated as: $\text{MAP} = \text{SAP}/3 + 2\text{DAP}/3$.

Cardiac output was measured with a pulsed Doppler system (2.25 MHz, Vingmed SD 50) 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 a time-motion recording (after visualization of a parasternal short-axis bidimensional view of the aortic valve). Then, the Doppler transducer was placed in the suprasternal notch and angulated to obtain the best signal which corresponds to the presumed axis 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 integrates Doppler signals and takes into account the 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 investigator variability was 1% and 3%, respectively whereas between investigators variability was 7% and 11%, respectively. Total peripheral resistance was calculated as the mean arterial pressure/cardiac output ratio.

Carotid artery haemodynamics Diameter and flow of the CCA (CCAD and CCABF, respectively) 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 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 arterial diameter. Then arterial mean blood velocity through the vessel cross-section was obtained by adjusting the gate to the corresponding arterial diameter and depth. The volumic blood flow (CCABF) was calculated using the formula:

$$\text{CCABF} = \pi \text{CCAD}^2 \cdot \text{Vm}/4,$$

where Vm is the mean blood flow velocity. CCAD values are the means of 4 consecutive measurements (2 with each transducer). For carotid blood velocity measurements, within investigator variability was 4% and between investigators variability was 11%.

Middle cerebral artery mean blood flow velocity (MCAmv)

This parameter was measured using the transcranial pulsed Doppler technique (Medasonics Transpect, 2 MHz). The Doppler probe was fixed over the right temple (where the resistance to ultrasound penetration is the lowest) using a special headset ensuring the stability of the device during the entire experimental period. Depth of focus was increased starting from 45 mm by 2 mm steps until bidirectional flow appeared (bifurcation of

the internal carotid artery). Then, this depth was progressively decreased until an exclusively positive signal, characteristic of the MCA was obtained, and until this signal reached its maximal value, indicating that the angle of incidence of the ultrasound beam with the blood flow axis was zero. The MCAmv was recorded over an 8 s period, at rest, in supine position, with no acoustic or visual distraction. Spectral analysis was accomplished with fast Fourier transformation, yielding MCAmv value. For these MCAmv measurements, within investigator variability was 3% and between investigators variability was 6%.

Biological parameters investigated were: plasma renin activity (PRA) which was assessed by radioimmunoassay (Ménard *et al.*, 1972), and plasma angiotensin I converting enzyme activity (PCEA) which was measured by a spectrophotometric method (Cushman & Cheung, 1971).

Experimental protocol

After an overnight fasting and a light breakfast at 06.00 h, each volunteer arrived at the laboratory at 07.00 h. An indwelling catheter was inserted into a forearm vein, the automatic monitor was immediately positioned around the contralateral arm, and the subject rested in the supine position. At 08.00 h, the control values of the clinical parameters (arterial blood pressure, heart rate, cardiac output, CCABF, CCAD and MCAmv) were assessed, and blood samples for determination of PRA and PCEA were collected.

At 08.30 h, the volunteer was given his treatment orally, together with 100 ml of water. Blood pressure was automatically recorded every 10 min from 07.00 h to 18.30 h and thereafter at 20.30 h, and 08.30, i.e. 24 h after drug intake. Heart rate was measured 1, 2, 3, 4, 6, 8, 10, 12 and 24 h after drug administration. MCAmv was recorded 1, 2, 3, 4, 6, 8 and 24 h after drug intake whereas the other clinical parameters were measured 2, 4, 8 and 24 h after drug administration. Finally, blood samples for PRA and PCEA determinations were collected 2, 4, 8, and 24 h after drug intake.

The volunteers were asked to remain at rest in the supine position during the whole duration of the experiments, except for two 30 min periods during which they were given a light standardized meal at 13.00 h and 19.00 h, respectively. No tea, coffee, alcohol, or smoking was allowed on the day before and during the whole trial

period. Finally the volunteer was asked at regular intervals to fill out a questionnaire as to his general tolerance to the drug.

Drug used

Ramipril 10 mg and the placebo were used as undistinguishable capsules.

Statistical analysis of the data

Results shown are absolute mean values $\pm$ s.e. mean.

In addition, differences between ramipril and placebo effects are indicated as mean percentages, followed if necessary, by the limits of the 95% confidence interval.

For each parameter: (a) basal values before each treatment were compared using a two-way analysis of variance (ANOVA), and (b) statistical analysis of the data obtained at different time intervals after administration of the two treatments was performed on the absolute values measured, using a three way analysis of variance followed, if significant, by a Newman-Keuls test.

Results

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

Systemic haemodynamics

Figures 1 and 2 illustrate the evolution with time of MAP, heart rate, cardiac output and total peripheral resistance during the 24 h following the administration of ramipril or placebo.

As can be seen, there was never any significant difference between the effects of ramipril and those of the placebo on these haemodynamic parameters. It must however be noticed that from 8 to 12 h after drug intake, ramipril induced a slight decrease in MAP (-7% (-1 to -13%) at 8 h) and in total peripheral resistance (-8% (-1 to -15%) at 8 h), but cardiac output remained unaffected ($+2\%$ (-3 to $+7\%$) at 8 h).

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

	Placebo	Ramipril
Systolic arterial pressure (mm Hg)	110.7 $\pm$ 2.0	110.8 $\pm$ 2.9
Diastolic arterial pressure (mm Hg)	58.3 $\pm$ 1.7	61.7 $\pm$ 1.6
Mean arterial pressure (mm Hg)	75.8 $\pm$ 1.3	78.1 $\pm$ 1.9
Heart rate (beats min ⁻¹)	66.5 $\pm$ 3.2	72.3 $\pm$ 3.5
Cardiac output (l min ⁻¹)	4.3 $\pm$ 0.2	4.3 $\pm$ 0.1
Total peripheral resistance (dyn s cm ⁻⁵)	1413 $\pm$ 66	1472 $\pm$ 43
Carotid blood flow (ml min ⁻¹)	266.6 $\pm$ 15.2	267.2 $\pm$ 11.7
Carotid artery diameter (mm)	5.28 $\pm$ 0.09	5.27 $\pm$ 0.07
Middle cerebral artery mean blood velocity (cm s ⁻¹)	68.2 $\pm$ 4.7	67.2 $\pm$ 3.7
Plasma converting enzyme activity (nmol min ⁻¹ ml ⁻¹)	18.0 $\pm$ 2.9	18.5 $\pm$ 2.6
Plasma renin activity (ng l ⁻¹ min ⁻¹)	24.2 $\pm$ 10.4	21.2 $\pm$ 7.0

Figure 1 Kinetics of mean arterial pressure (mm Hg) and heart rate (beats min⁻¹) values during the 24 h period following oral administration of either ramipril (●) or placebo (□). Vertical lines show the s.e. mean.

Figure 2 Kinetics of total peripheral resistance (dyn s cm⁻⁵) and cardiac output (l min⁻¹) values during the 24 h period following oral administration of either ramipril (●) or placebo (□). Vertical lines show the s.e. mean.

Figure 3 Kinetics of carotid blood flow (ml min⁻¹), carotid artery diameter (mm), and middle cerebral artery mean blood flow velocity (cm s⁻¹) values during the 24 h period following oral administration of either ramipril (●) or placebo (□). Vertical lines show the s.e. mean with a significant difference between ramipril and placebo shown as **, *P* at least < 0.01.

Middle cerebral artery mean blood flow velocity

As shown in Figure 3, the evolution with time of MCAMv was strictly similar after ramipril and placebo. Spontaneous variations were observed after the placebo, i.e. a decrease (−19%) at 3 h. These variations were not influenced by ramipril. For example, at the time of ramipril-induced maximal increase in CCABF (8 h), there was no significant difference between ramipril and placebo effects on MCAMv (+2.5% (−7.4 to +12.4%)).

Biological parameters (Figure 4)

Ramipril induced a strong and long lasting PCEA inhibition. This effect reached its maximum (with an average inhibition of 96%, *P* < 0.01) at 4 h and was still significant (−63%, *P* < 0.01) after 24 h.

Ramipril also induced an increase in PRA that began 2 h after drug intake (+493%), was statistically significant after 4 h, peaked at 8 h (+993%, *P* < 0.01), and was still observed after 24 h (+236%, NS).

Carotid haemodynamics

As shown in Figure 3, ramipril significantly increased CCABF from 4 (+17% (+9 to +25%), *P* < 0.01) to 8 h (+27% (+20 to +34%), *P* < 0.01) after drug intake. Simultaneously, there was a slight but non-significant increase in CCAD (+2.3% (−1.3 to +5.9%)) at 8 h.

Figure 4 Kinetics of plasma converting enzyme ($\text{nmol min}^{-1} \text{ml}^{-1}$) and renin ($\text{ng l}^{-1} \text{min}^{-1}$) activities values during the 24 h period following oral administration of either ramipril (●) or placebo (□). Vertical lines show the s.e. mean with a significant difference between ramipril and placebo shown as *, $P < 0.05$, and **, P at least < 0.01 .

Tolerance

No serious untoward effects were encountered during this study. Moderate headache was spontaneously reported by two subjects in the ramipril group.

Discussion

Transcranial Doppler technique

As previously mentioned, available techniques for cerebral blood flow measurement which are either invasive and/or imply the use of radioactivity, cannot easily be used for multiple measurements and hence for the assessment of the kinetics of a drug's effects in healthy volunteers. In contrast, the transcranial Doppler technique is a newly developed method that allows repeated measurements of blood flow velocity in large intracranial arteries, and especially in the middle cerebral artery (MCA). The latter, being in its initial part directly directed to the temporal bone, it is easy to bring into alignment the ultrasound beam and the MCA axis. Hence, given the Doppler equation, one can accurately determine the actual flow velocity inasmuch as the incidence angle θ between the ultrasound beam and the MCA axis being nil, $\cos \theta$ equals 1. Using this method-

ology, within investigator and between investigators variabilities were found to be 3% and 6%, respectively.

The transcranial Doppler technique does not allow measurements of the absolute blood flow value in the MCA inasmuch as the diameter of this vessel cannot be determined. And it must be kept in mind that cerebral arteries' diameter may vary. In anaesthetized dogs, Busija *et al.* (1981) have shown that severe hypercapnia (60 mm Hg) associated with hypertension results in an increase in large pial arteries' diameter. More recently, Fujii *et al.* (1991) have demonstrated in rats a flow-dependent vasodilation of the basilar artery in response to experimentally induced 100 to 200% increases in local flow. But in all these studies, modifications of the large vessels' diameter were observed only when extreme alterations of the haemodynamic conditions were achieved, which was certainly not the case in our study.

Anyhow, it has clearly been demonstrated both in animal experiments (Martin *et al.*, 1990) and in clinical studies (Piepgras *et al.*, 1991) that the changes of large cerebral arteries' blood flow velocity are correlated to those in cerebral blood flow with enough accuracy to be used in clinical studies (Kontos, 1989).

As can be seen from our data, MCAmv values varied with time during the placebo period. These changes (a) occurred although the measurements were always performed by the same investigator and under the same experimental conditions, i.e. at rest, before blood sampling and before determination of the other parameters, (b) were observed in all subjects with the same kinetics, and (c) were large enough to exceed the variability of the measurement technique. It must be noticed that the changes observed in MCAmv occurred together with variations in arterial blood pressure. However, because of cerebral blood flow autoregulation, it is unlikely that the former were related to the latter. These findings could indicate a diurnal variation of MCAmv but further experiments are necessary to confirm or invalidate this hypothesis.

Effects of ramipril

In this study, and as expected from previous experiments (Manhem *et al.*, 1985; Thuillez *et al.*, 1987; Witte *et al.*, 1984), ramipril produced a potent and long lasting PCEA inhibition as well as the classically accompanying increase in PRA.

In our salt-replete normotensive subjects, ramipril exerted almost no effect on systemic haemodynamics. Arterial blood pressure was slightly lowered between 6 and 10 h after drug intake and heart rate was not modified. These data are in agreement with previous ones obtained in healthy volunteers with ramipril (Thuillez *et al.*, 1987) as well as with other ACEIs (Richer *et al.*, 1987; Thuillez *et al.*, 1991a). In addition, cardiac output was not modified and hence the slight reduction in arterial blood pressure was exclusively due to that, also moderate, of total peripheral resistance.

Also confirming previous findings (Thuillez *et al.*, 1987), ramipril induced a strong and significant increase in CCABF which, given the almost unchanged arterial blood pressure value, indicates arteriolar vasodilation. Simultaneously, ramipril had almost no effect on CCAD, indicating that it does not dilate the large conductance

vessels of the carotid vascular bed. This finding is in agreement with the results obtained in previous studies with ramipril (Thuillez *et al.*, 1987) and other ACEIs (Richer *et al.*, 1987; Thuillez *et al.*, 1991a), but contrasts with what is observed in other vascular territories, e.g. the brachial vascular bed in which all ACEIs dilate the large conductance vessels (Richer *et al.*, 1987; Thuillez *et al.*, 1987, 1991a). Inasmuch as CCABF is strongly augmented by ramipril, the lack of simultaneous CCAD increase is surprising and suggests (a) that ACEIs do not exert any direct vasodilating effect on the carotid large conductance vessels, and (b) that the indirect flow-mediated vasodilating mechanism is only poorly operating at this level. Anyhow, ACEIs appear to exhibit a pattern of vasodilating effects in the carotid vascular bed which distinguishes them from other vasodilators, e.g. nicardipine (Thuillez *et al.*, 1984) and pinacidil (Thuillez *et al.*, 1991b) which in healthy volunteers do increase simultaneously and significantly CCABF and CCAD.

It appears from our data that there was no difference between the effects of ramipril and those of the placebo

on MCAmv. Furthermore, ramipril did not modify the spontaneous evolution of this parameter seen under placebo. With all the limitations discussed above, and assuming that MCA diameter was not drug-affected, our results tend to indicate that ramipril, in the dose of 10 mg, does not modify MCA blood flow and by extrapolation cerebral blood flow in the healthy volunteer. Thus these data confirm previous ones obtained, using different techniques, with captopril (Schmidt *et al.*, 1990; Waldemar *et al.*, 1984).

In conclusion, it appears that in a dose that produces an important PCEA blockade and that strongly increases carotid and peripheral blood flows in healthy volunteers, ramipril does not affect MCA blood flow velocity and probably cerebral blood flow, thus suggesting that ACEI-induced arteriolar vasodilation in the carotid territory only concerns the extracranial part of this muscular and cutaneous vascular bed.

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