Effects of acute and chronic cilazapril treatment in spontaneously hypertensive rats

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1 The effects of acute and chronic treatment with cilazapril, a new ACE inhibitor, on peripheral vasculature and renal excretory function were assessed in spontaneously hypertensive rats. Regional blood flow and cardiac output were measured by the radioactive microspheres technique.

2 Acute treatment (3 mg kg^{-1} intravenously) reduced mean arterial blood pressure from 171 ± 7 to $140 \pm 7 \text{ mm Hg}$ ($P < 0.001$), chronic treatment ($1 \times 10 \text{ mg kg}^{-1} \text{ day}^{-1}$ orally for 9 weeks) from 191 ± 5 to $122 \pm 3 \text{ mm Hg}$ ($P < 0.001$). With both kinds of treatments cardiac output was unchanged. Heart rate was slightly decreased (-9% , $P < 0.05$) with chronic treatment. Acutely, the main effect of cilazapril was a decrease of the renal vascular resistance (-41% , $P < 0.001$) associated with an increase of the fraction of the cardiac output distributed to the kidney ($+46\%$, $P < 0.001$). Chronically, cilazapril decreased regional vascular resistance in most of the peripheral vascular beds except the heart.

3 With a high dose of cilazapril (10 mg kg^{-1} orally) both acute and chronic treatment increased diuresis ($+107\%$ and $+92\%$, $P < 0.001$) and natriuresis ($+124\%$ and $+111\%$, $P < 0.001$) with a slight increase in kaliuresis. However, with a low dose (1 mg kg^{-1} orally) the kidneys responded only to chronic treatment.

4 It is concluded that chronic treatment with cilazapril decreases arterial blood pressure more than acute treatment. This effect seems to be due to a greater peripheral vasodilation. In addition, diuretic and natriuretic effects of cilazapril probably contribute to blood pressure reduction.

Keywords cilazapril angiotensin-converting enzyme inhibitor regional blood flows kidney excretory function

Introduction

Cilazapril is a new angiotensin-converting enzyme (ACE) inhibitor (Attwood *et al.*, 1984) which effectively reduces arterial blood pressure in spontaneously hypertensive rats (SHR) (Natoff *et al.*, 1985; Hefti *et al.*, 1986; Clozel & Hefti, 1987; Clozel *et al.*, 1987; Nakamura *et al.*, 1988) as well as in volume-depleted normotensive and renal hypertensive dogs (Holck *et al.*, 1986).

Chronic ACE inhibition was shown not only to lower blood pressure in adult SHR with established hypertension (Laffan *et al.*, 1978; Muirhead *et al.*, 1978; Ferrone & Antonaccio, 1979; Clozel *et al.*, 1989), but also to prevent the development of hypertension in growing SHR (Ferrone & Antonaccio, 1979; Giudicelli *et al.*, 1980a, b; Richer *et al.*, 1982; Hefti *et al.*, 1986).

The hypotensive effect in this animal model seemed to be mainly due to a reduction in peripheral vascular resistance (Muirhead *et al.*, 1978; Koike *et al.*, 1980; Hefti *et al.*, 1986; Clozel & Hefti, 1987; Clozel *et al.*, 1987). In hypertensive patients, ACE inhibition reduced in parallel blood pressure and peripheral vascular resistance in kidney, skeletal muscle, skin and the splanchnic organs (Ventura *et al.*, 1985).

Another contribution of ACE inhibitors to their hypotensive action may be their effects on renal excretory function. ACE inhibition was shown to induce natriuresis and diuresis in various experimental models (McCaa *et al.*, 1978; Atlas *et al.*, 1979; Hollenberg *et al.*, Brunner *et al.*, 1981; Mijamoto *et al.*, 1981; De Zeeuw *et al.*, 1983; Sweet *et al.*, 1983; Düsing *et al.*, 1985; Becker & Schölkens, 1987) which may be due to a direct effect on the kidney or, indirectly, due to inhibition of aldosterone secretion secondary to reduction of angiotensin II. It has previously been shown that cilazapril increases sodium and water excretion acutely in conscious normotensive dogs (Holck *et al.*, 1986).

The aim of the present study was to compare the effects of acute and chronic cilazapril treatment in SHR with regard to peripheral vasodilation and kidney function.

Methods

Regional blood flow and cardiac output were measured with radioactive microspheres 15 μ m in diameter according to the reference sample technique (Heymann *et al.*, 1977). Four hours before the measurement of regional blood flows, under ether anaesthesia, polyethylene catheters (PE 50 and PE 10) were placed in the left ventricle via the right carotid artery for injecting the microspheres and in the femoral artery for arterial pressure measurement and reference blood sample withdrawal.

Arterial blood pressure, measured before each injection of microspheres through the femoral arterial catheter, and heart rate, obtained from the arterial pressure trace with a tachymeter, were recorded on a Gould Brush recorder.

Regional blood flow and cardiac output were calculated according to standard procedure (Clozel & Hefti, 1987). Regional vascular resistance was calculated as mean arterial pressure divided by regional blood flow, total vascular resistance as mean arterial pressure divided by cardiac output (fractional distribution of cardiac output).

Measurement of regional blood flow and haemodynamics

In an *acute* study 3 month-old male SHR from the Okamoto strain (SP/A3N) were used. One group of nine rats received intravenously 3 mg kg⁻¹ of cilazapril, another group of seven rats were given vehicle (control group). All the variables were measured 15 min after injection at the maximal haemodynamic responses. Preliminary studies had shown that such an intravenous dose completely inhibited the response to injected AI.

In a *chronic* study 4-week-old male SHR were used. One group of 11 rats received, by oral gavage at the same time every day, a single dose of cilazapril in distilled water (10 mg kg⁻¹) for 9 weeks. Another group of 12 rats, used as controls, received only distilled water. The parameters were measured 5 h after the last cilazapril administration.

Measurement of urine and electrolyte excretion

Groups of SHR (SP/A3N) weighing 280 – 300 g (14 weeks of age) were used. Four groups of 10 SHR receiving cilazapril (1 and 10 mg kg⁻¹ orally in 0.9% NaCl, 10 mg kg⁻¹) either once (*acute*) or for 7 days (*chronic*), were compared with a control group ($n = 20$) receiving only the vehicle. All animals were maintained under identical conditions and had free access to normal rat chow and water. Urine and cation measurements were carried out with rats fasted overnight. Urine was sampled for 5 h, starting immediately after the cilazapril gavage. Cation content (Na⁺, K⁺) were analyzed by flame photometry (model CORNING EEL 450) from a 5 h collecting sample.

Statistical analysis

All results are expressed as mean $\pm$ s.e.mean. The treatment groups were compared to the respective control group using unpaired Student's *t*-test.

Results

Haemodynamic effects of cilazapril

Acute treatment with cilazapril (3 mg kg⁻¹ intravenously) reduced mean arterial pressure from 171 ± 7 to 140 ± 4 mm Hg ($P < 0.001$), chronic treatment (1×10 mg kg⁻¹ day orally for 9 weeks) from 191 ± 5 to 122 ± 3 mm Hg ($P < 0.001$) (Table 1). Heart rate was unchanged in

Table 1 Haemodynamic effects of cilazapril in SHR

		Control (A: n = 7) (C: n = 12)	Cilazapril (A: n = 9) (C: n = 11)	Δ (%)
SAP (mm Hg)	A	194 $\pm$ 6	161 $\pm$ 4	-17***
	C	215 $\pm$ 3	135 $\pm$ 3	-37***
DAP (mm Hg)	A	147 $\pm$ 7	121 $\pm$ 5	-18***
	C	167 $\pm$ 5	107 $\pm$ 4	-37***
MAP (mm Hg)	A	171 $\pm$ 7	140 $\pm$ 4	-18***
	C	191 $\pm$ 5	122 $\pm$ 3	-36***
CO (ml min ⁻¹ kg ⁻¹)	A	287 $\pm$ 28	301 $\pm$ 14	+ 5
	C	322 $\pm$ 23	331 $\pm$ 11	+ 3
HR (beats min ⁻¹)	A	389 $\pm$ 14	407 $\pm$ 12	+ 5
	C	440 $\pm$ 14	401 $\pm$ 9	- 9*
TVR (mm Hg $\times$ min ml ⁻¹ kg ⁻¹)	A	6.31 $\pm$ 0.62	4.81 $\pm$ 0.32	-24***
	C	6.12 $\pm$ 0.41	4.10 $\pm$ 0.11	-33***
SAP	Systolic arterial pressure			
DAP	Diastolic arterial pressure			
MAP	Mean arterial pressure			
CO	Cardiac output			
TVR	Total vascular resistance			
HR	Heart rate			
A	Acute treatment: 1 $\times$ 3 mg kg ⁻¹ intravenously			
C	Chronic treatment: 1 $\times$ 10 mg kg ⁻¹ day ⁻¹ orally for 9 weeks			

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs control group.

the acute experiment but slightly reduced under chronic treatment (-9% , $P < 0.05$). With both kinds of treatment cardiac output was unchanged. Total vascular resistance was less reduced in the acute (-24% , $P < 0.001$) than in the chronic experiment (-33% , $P < 0.001$)

Effects of cilazapril on regional blood flows and regional vascular resistances

The absolute values of regional blood flows (RBF), regional vascular resistances (RVR) and fractional distribution of cardiac output (FDCO) for the acute treatment are given in Table 2, the values for the chronic treatment have been published before in detail (Clozel & Hefti, 1987; Clozel *et al.*, 1987). The changes of RBF, RVR and FDCO with both acute and chronic treatments are summarized in Figure 1.

There are several differences between acute and chronic cilazapril treatment with regard to RBF, RVR and FDCO (Figure 1a, b, c). In the acute experiment RBF was increased in kidneys ($+40\%$, $P < 0.001$) and skin ($+39\%$, NS). The RBFs of most of the other organs tended to decrease. However, this decrease was significant only in brain. RVRs tended to decrease in general. The largest decreases were seen in kidney (-41% , $P < 0.001$), skin (-41% , NS) and diaphragm (-21% , $P < 0.05$).

In contrast to the acute experiment, chronic treatment with cilazapril produced peripheral vasodilation in most of the vascular beds. RVR was decreased in all the peripheral vascular beds except the heart. The largest decreases were observed in kidney (-50% , $P < 0.001$), skin (-56% , $P < 0.001$) and the splanchnic organs. In parallel RBFs increased in skin ($+40\%$, $P < 0.05$), stomach ($+41\%$, $P < 0.05$) and kidneys ($+26\%$, $P < 0.05$). In heart, coronary blood flow was significantly decreased. There was no change of cardiac RVR.

Cilazapril affected FDCO differently in the acute and the chronic experiments (Figure 1c). Acutely, it induced changes in kidney ($+46\%$, $P < 0.001$) and brain (-30% , NS). Chronically, however, it mainly changed FDCO in heart (-45% , $P < 0.001$) and stomach ($+38\%$, $P < 0.01$), whereas the increase in the kidneys was much less ($+13\%$, NS) and cerebral blood flow was unaffected.

Effects of cilazapril on urine and electrolyte excretion

With a high dose of cilazapril (10 mg kg⁻¹ orally) both acute and chronic treatment increased diuresis ($+107\%$ and $+92\%$, $P < 0.001$) and natriuresis ($+124\%$ and $+111\%$, $P < 0.001$) without significantly changing kaliuresis (Table

Table 2 Effects of acute cilazapril treatment on regional blood flows, resistances and fractional distribution of cardiac output

Organ	RBF		RVR		FDCO	
	Control (n = 7)	Cilazapril (n = 9)	Control (n = 7)	Cilazapril (n = 9)	Control (n = 7)	Cilazapril (n = 9)
Brain	1.54 ± 0.12	1.13 ± 0.07**	115 ± 8	129 ± 8	2.37 ± 0.20	1.66 ± 0.14
Heart	9.26 ± 0.89	7.54 ± 0.36	28 ± 4	26 ± 1	9.26 ± 0.89	7.54 ± 0.36
Kidneys	6.83 ± 0.53	9.61 ± 0.56***	27 ± 3	16 ± 1***	19.54 ± 1.17	28.53 ± 1.17***
Diaphragm	0.61 ± 0.05	0.65 ± 0.07	292 ± 26	232 ± 25*		
Skeletal muscle	0.21 ± 0.05	0.17 ± 0.02	1061 ± 190	1063 ± 147		
Liver	0.05 ± 0.01	0.05 ± 0.01	3693 ± 576	2967 ± 284		
Stomach	1.72 ± 0.24	1.53 ± 0.20	113 ± 16	104 ± 13	2.16 ± 0.16	1.96 ± 0.20
Duodenum	3.43 ± 0.47	2.70 ± 0.11	56 ± 7	53 ± 3		
Colon	2.47 ± 0.44	1.84 ± 0.25	85 ± 16	82 ± 11		
Skin	0.18 ± 0.03	0.25 ± 0.02	1103 ± 143	647 ± 60		

RBF Regional blood flow (ml min⁻¹ g⁻¹)RVR Regional vascular resistance (mm Hg min ml⁻¹ g⁻¹)

FDCO Fractional distribution of cardiac output (%)

Acute treatment: 3 mg kg⁻¹ intravenously**P* < 0.05, ***P* < 0.01, ****P* < 0.001 vs control group.**Table 3** Effects of cilazapril on urine and electrolyte excretion

		Control	Cilazapril	
			(1 mg kg ⁻¹ p.o.)	(10 mg kg ⁻¹ p.o.)
Na ⁺ (μmol kg ⁻¹ 5 h ⁻¹)	A	1200 ± 119	127 ± 110	2682 ± 126***
	C	941 ± 82	1969 ± 111***	1984 ± 104***
K ⁺ (μmol kg ⁻¹ 5 h ⁻¹)	A	314 ± 23	287 ± 42	330 ± 24
	C	246 ± 20	345 ± 35*	317 ± 40
U (ml kg ⁻¹ 5 h ⁻¹)	A	10.1 ± 0.7	9.7 ± 0.7	20.9 ± 0.6***
	C	8.4 ± 0.6	12.4 ± 0.7**	16.1 ± 0.8***

A Acute treatment: 1 × 10 mg kg⁻¹ orallyC Chronic treatment: 1 × 10 mg kg⁻¹ day orally for 7 days**P* < 0.05, ***P* < 0.01, ****P* < 0.001 vs control group.

3, Figure 2). However, with a low dose (1 mg kg⁻¹ orally), diuresis and natriuresis increased only under chronic treatment for 7 days (+48%, *P* < 0.01 and +109%, *P* < 0.001, respectively), in parallel with a slight increase in potassium excretion (+40%, *P* < 0.05).

Discussion

Our study confirms that cilazapril treatment is very effective in reducing arterial blood pressure in adult SHR with a concomitant reduction in total peripheral resistance. However, maximal decreases were not reached after acute treatment but only after repetitive administration. Similar findings have been reported before in conscious renal hypertensive dogs (Holck *et al.*, 1986).

Hypertension in SHR seems not to be due to high circulating renin (Trippodo & Frolich, 1981)

but rather to increased vascular renin and ACE activity compared with the WKY controls (Asaad & Antonaccio, 1982; Dzau, 1984; Mizuno *et al.*, 1986; Nakamura *et al.*, 1988). Indeed, the anti-hypertensive effect of ACE inhibition in SHR is thought to be due to inhibition of vascular angiotension II production as the fall in blood pressure is closely related to inhibition of vascular ACE activity (Cohen *et al.*, 1983; Unger *et al.*, 1984, 1985) and not to inhibition of the plasma system. These findings are substantiated by the study of Wilkes (1984), who found a sustained blood pressure reduction in SHR during chronic treatment with the ACE inhibitor enalapril even though plasma angiotension II levels recovered. Nakamura *et al.* (1988) showed that cilazapril was able to reduce the ACE activity in all major vessels of SHR. Thus, inhibition of the vascular renin-angiotensin system by cilazapril may lead to peripheral vasodilation and thus to blood pressure decrease in SHR.

Figure 1 Changes of regional blood flows (a), resistance (b) and fractional distribution of cardiac output (c) with acute (open bars) and chronic (filled bars) cilazapril treatment. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; a, s.e.mean equals $\pm 90\%$.

Indeed, cilazapril dilated most of the peripheral vascular beds (Figure 1b). However, with chronic treatment, the dilation was more pronounced (especially in the splanchnic beds) than with acute treatment, in parallel with the blood pressure decrease. Even though plasma ACE activity was not measured in this study directly, we assume that the acute dose of 3 mg kg^{-1}

Figure 2 Changes of urine (U) and electrolyte (Na⁺, K⁺) excretion with acute (single dose of 1 or 10 mg kg⁻¹ p.o.; open bars) and chronic (once daily 1 or 10 mg kg⁻¹ p.o. per day for 7 days; filled bars) cilazapril treatment. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

intravenously inhibits the plasma system completely, because of the maximal suppression of AI pressure response (data not shown). Therefore, the additional blood pressure reduction after chronic ACE inhibition with cilazapril cannot be explained by a further reduction of angiotension II.

In brain, the initial decrease of RBF was normalized with chronic treatment by a pronounced vasodilation. This cerebral vasodilation could be caused by a direct effect of cilazapril or by autoregulatory mechanism(s) set to maintain constant blood flow despite the decrease in arterial pressure (Rapela & Green, 1964).

The only organ with no vasodilation and with a significantly decreased RBF was the heart. Coronary blood flow is closely linked to myocardial oxygen consumption (Belloni & Sparks, 1977), and cilazapril affected two of the main factors of this oxygen consumption: mean arterial pressure and heart rate (Sarnoff *et al.*, 1958). Coronary blood flow was considerably more decreased after chronic than after acute treatment, which can be explained by a stronger reduction in pressure and, in addition, a negative

chronotropic effect. Thus, the decrease in coronary blood flow is probably due to a decrease in myocardial oxygen consumption.

In addition to vasodilation 10 mg kg^{-1} oral cilazapril caused a marked diuresis and natriuresis both acutely and chronically. After chronic treatment, this was associated with a slight kaliuresis. However, at a low dose (1 mg kg^{-1} orally) of cilazapril, increased diuresis and natriuresis were observed only after prolonged treatment, thus also revealing long-term effects as for regional peripheral resistances.

One possible explanation for the natriuretic/diuretic effect of ACE inhibitors is the inhibition of aldosterone secondary to a reduction of angiotensin II (McCaa *et al.*, 1978; Atlas *et al.*, 1979; Brunner *et al.*, 1981). However, ACE inhibition induced natriuresis even in adrenalectomized animals (Sweet *et al.*, 1983). Reduced aldosterone secretion may thus not be solely responsible for the natriuretic/diuretic effects observed in this study but rather the direct changes in renal haemodynamics. This would explain also the slight kaliuresis seen during chronic treatment with cilazapril. Interestingly, this parallels the study of McNabb *et al.* (1986) who observed a slight kaliuresis with enalapril in man.

Overall, the findings suggest that short-term and long-term reductions of blood pressure in SHR are governed in part by the same and in part by different mechanisms. Blood pressure changes reflect the net effect of a large number of variables. For *acute* effects the contributions of cardiac output, heart rate and peripheral resistance are most prominent. It is noteworthy that cilazapril seems to lower blood pressure acutely by reducing peripheral resistance without changing cardiac output and heart rate. This lack of reflex tachycardia, which has been observed with other ACE inhibitors (Antonaccio, 1982), may be advantageous in hypertensive patients with coronary artery disease. Furthermore, additional contributions of changes in plasma volume and plasma ion concentrations such as

those described here with cilazapril may come into play. The observed diuretic/natriuretic effect with ACE inhibition may not only help to reduce blood pressure further but may be helpful in congestive heart failure patients. Indeed, ACE inhibitors seem to be very effective in this disease (Cody, 1986; The Consensus Trial Study Group, 1987).

Long-term effects of ACE inhibitors, finally, may include effects on cellular growth. Angiotensin II has been shown to induce increased protein synthesis in cells such as cardiac myocytes (Khairallah *et al.*, 1972) and was shown to increase growth rates and cell sizes in cultured smooth muscle cells (Campbell-Boswell & Robertson, 1981). In fact, cardiac hypertrophy was decreased by ACE inhibitors (Owens, 1987; Di Bello *et al.*, 1987) including cilazapril (Hefti *et al.*, 1986; Clozel & Hefti, 1987; Clozel *et al.*, 1987) but not by hydralazine, propranolol (Owens, 1987) or hydrochlorothiazide (Fernandez *et al.*, 1984). Furthermore, cilazapril seemed to reduce markedly the hypertrophic coronary vasculature in SHR with established hypertension and to improve the coronary vascular reserve (Clozel *et al.*, 1989). This observation is paralleled by the study of Owens (1987) who demonstrated a decrease of aortic medial hypertrophy in SHR by captopril but interestingly not by propranolol, even though both lowered arterial blood pressure.

Taken together, the results of our study show that cilazapril reduces blood pressure in SHR more with chronic than with acute treatment. The explanation appeared to be a more pronounced peripheral vasodilation with time. An increased renal excretory effect of cilazapril probably contributes to the antihypertensive effect.

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