The effect of acute ACE inhibition on atrial natriuretic peptide

C. J. DOORENBOS & P. VAN BRUMMELEN

Hypertension Research Unit, Department of Nephrology, Leiden, Netherlands

1 The effect of acute angiotensin converting enzyme (ACE) inhibition on the plasma concentrations of atrial natriuretic peptide (ANP) was investigated in a single-blind placebo controlled crossover study in healthy volunteers.

2 Intravenous infusion of 2 mg cilazaprilat resulted in a significant and short lasting inhibition of ACE as evidenced by a decrease of plasma angiotensin II and an increase in plasma renin activity.

3 When compared with placebo cilazaprilat lowered diastolic pressure and increased heart rate significantly.

4 No effect of cilazaprilat was found on plasma ANP levels, suggesting that angiotensin II does not mediate ANP release.

Keywords atrial natriuretic peptide angiotensin converting enzyme inhibition cilazaprilat

Introduction

In the last few years it has become evident that atrial natriuretic peptide (ANP) is involved in the regulation of body fluid volumes and possibly blood pressure as well, via a natriuretic and diuretic effect and via the ability to relax vascular smooth muscle (Needleman & Greenwald, 1986). Furthermore, it has become clear that ANP is closely connected to the renin-angiotensin-aldosterone system through various mechanisms including (1) inhibition of the release of renin (Kurtz *et al.*, 1986), (2) opposition to the sodium retaining effect of angiotensin II (McMurray & Struthers, 1988), (3) blockade of the synthesis and release of aldosterone (Higuchi *et al.*, 1986), (4) blockade of the sodium retaining effect of aldosterone (Mantero *et al.*, 1987) and (5) opposition to the vasoconstrictor effect of angiotensin II (Maack *et al.*, 1985). Despite this close relationship, few studies have been reported in the literature on the effects of blockade of the renin-angiotensin-aldosterone system by converting enzyme inhibitors on the pharmacological actions or plasma levels of ANP.

It has been shown in Wistar rats that the natriuretic action of infusion of ANP is not influenced by pretreatment with captopril (Hirata *et al.*, 1987). Data on the influence of converting enzyme inhibition on the hypotensive effect of an ANP infusion are inconsistent since both a potentiation (Awah *et al.*, 1986) and no effect (Hirata *et al.*, 1987; Hansell & Ulfendahl, 1987; Gaillard *et al.*, 1988) have been reported. Finally, it has recently been shown in humans that the vasodilatory effect of an intra-arterial infusion of ANP is not influenced by pretreatment with captopril (Hughes *et al.*, 1988).

With regard to the effects on the plasma levels of ANP, reductions have been reported after acute converting enzyme inhibition in normotensive rats (Iwao *et al.*, 1987) and after chronic treatment with captopril or enalapril in spontaneously hypertensive rats (Kohnno *et al.*, 1987). In man a reduction in plasma ANP levels was found in healthy volunteers on a low sodium diet after 1 week of treatment with enalapril (Mann *et al.*, 1986) whereas no change was found in

hypertensive patients who had been treated with enalapril for a period of 4 weeks (Chalmers *et al.*, 1986). The mechanisms underlying these apparent differences remain to be clarified.

We report on a pilot study in young healthy volunteers on the effects of acute converting enzyme blockade with intravenous cilazaprilat on the plasma concentrations of ANP.

Methods

Subjects

Six healthy male volunteers were studied. They had normal blood pressures and no abnormalities in medical history, physical examination or screening laboratory tests, including haemoglobin, electrolytes, liver enzymes and urinalysis.

Study protocol

The study protocol was approved by the Hospital Committee on Medical Ethics and all subjects gave their informed consent. Each subject was studied twice with an interval of at least 5 days. Urine was collected in the 24 h preceding each study for determination of creatinine and sodium. All studies were performed in a quiet room in the morning, after subjects consumed a light breakfast. They were asked to abstain from smoking and consumption of alcohol or caffeine containing beverages for at least 12 h before the study. The subjects lay on a bed throughout the study, except for voiding urine. An indwelling cannula was placed in an antecubital vein for blood sampling and for the infusion of the drug or placebo. After emptying the bladder the subjects lay supine on a bed for 30 min, when the basal blood sample was taken. Then the study drug was administered over a 10 min period with a rate controlled infusion pump. Either 2 mg cilazaprilat in 10 ml saline or 10 ml saline alone was infused in a single blind randomized fashion. Blood samples were taken at 5, 15, 45 and 135 min after the end of the infusion. After the last two samples the subjects voided urine in the upright posture.

Determinations

Blood pressure and heart rate were recorded with a Dinamap (Critikon Inc., Tampa, Florida) at regular intervals. The mean value of three determinations before each blood sampling was calculated. Routine biochemical determinations (sodium, potassium, creatinine, protein, uric

Figure 1 Mean values ($\pm$ s.e. mean) of the haemodynamic effects of cilazaprilat infusion (closed circles, C) compared with placebo infusion (open circles, P). Compared with placebo, cilazaprilat had a significant effect on diastolic blood pressure and heart rate as indicated, but not on systolic blood pressure, by analysis of variance. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ compared with basal values (B), by MANOVA.

acid) were performed using an Auto Analyzer. Plasma renin activity, aldosterone and angiotensin II were determined by radioimmunoassay. Plasma noradrenaline levels were measured by a single isotope radioenzymatic assay (Peuler & Johnson, 1977). The intra-assay coefficient of variation in our laboratory was 5% in the 0.5 nmol l^{-1} range for both adrenaline and noradrenaline. Plasma ANP was determined by radioimmunoassay after extraction of the plasma with Sep-Pak C18 cartridges (Doorenbos *et al.*, 1987). The recovery was $90.8 \pm 5.0\%$ (mean $\pm$ s.d., $n = 10$) and the intra-assay and interassay variations were 5% and 6% respectively.

Statistical analysis was performed by multivariate analysis of variance with correction for repeated measurements (MANOVA), using the SAS-PC computer programme.

Figure 2 Mean values ($\pm$ s.e. mean) of urinary sodium excretion per hour in the 24 h before the study (B) and during the first and second collection period of the study for cilazaprilat (closed circles, C) and placebo (open circles, P). The difference was not significant by analysis of variance, and the study periods were not significantly different from the control period, by MANOVA.

Figure 3 Mean values ($\pm$ s.e. mean) of plasma ANP levels after cilazaprilat infusion (closed circles, C) and placebo (open circles, P). Cilazaprilat had no significant effect compared with placebo by analysis of variance and the post-infusion values were not significantly different from basal values (B), by MANOVA.

Results

The intravenous infusion of cilazaprilat was well tolerated by all subjects and no adverse effects were noted. As shown in Figure 1, blood pressure fell slightly after placebo, but cilazaprilat caused a marked fall of especially the diastolic blood pressure, which was accompanied by a significant increase of heart rate. The haemodynamic effects were short-lasting and had almost disappeared 135 min after the infusion.

The urinary sodium excretion in the 24 h before each study day was similar, as shown in

Figure 4 Mean values ($\pm$ s.e. mean) of the effects of cilazaprilat infusion on the renin-angiotensin-aldosterone system (closed circles, C) compared with placebo infusion (open circles, P). Compared with placebo, cilazaprilat had a significant effect on plasma renin activity and angiotensin II as indicated, but not on plasma aldosterone, by analysis of variance. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ compared with basal values (B), by MANOVA.

Figure 2. Cilazaprilat caused a small increase of sodium excretion which persisted in the period from 45 to 135 min after the infusion, but this increase did not reach statistical significance. Figure 3 displays the plasma ANP concentrations. No significant change was found between cilazaprilat and placebo, and neither infusion had an effect on the plasma ANP concentrations. In Figure 4 the results of the infusions on the renin-angiotensin-aldosterone system are depicted. Cilazaprilat caused a short-lasting decrease of angiotensin II, accompanied by a rise of the plasma renin activity. Plasma aldosterone decreased significantly in both instances, and there was no difference between the two infusions.

Discussion

In this study the infusion of cilazaprilat resulted in an acute and short-lasting blockade of the angiotensin converting enzyme, as evidenced by the decrease in the angiotensin II concentration which did not occur after the placebo infusion. Furthermore, the plasma renin activity showed a clear rise. The fact that the plasma aldosterone concentration decreased also after the placebo infusion may be explained by the circadian rhythm of aldosterone secretion, which is related to the circadian rhythm of ACTH (Katz *et al.*, 1975). The spontaneous decline of plasma aldosterone in the morning may have masked the expected aldosterone lowering effect of cilazaprilat.

The inhibition of the angiotensin converting enzyme resulted in a marked lowering of the blood pressure, particularly the diastolic pressure, which was accompanied by a compensatory increase of the heart rate.

Despite these marked effects on the renin-angiotensin-aldosterone system and on the haemodynamic systems, the plasma levels of ANP were similar after cilazaprilat and placebo infusion. Atrial stretch plays a role in most conditions associated with an elevated plasma ANP level, such as volume expansion, congestive heart failure, hypertension and tachycardia (Needleman & Greenwald, 1986). It has been reported that a change from the upright to the supine posture is accompanied by an initial

increase in the plasma levels of ANP, reaching a maximum value after 30 min, followed by a slight decline over the next several hours (Solomon *et al.*, 1986). This sequence of events is consistent with our results after the placebo infusion, since the first blood sample was taken after 30 min rest in the supine position. Although the arterial blood pressure fell after cilazaprilat infusion, the expected lowering of plasma ANP may have been offset by the accompanying tachycardia. Our results are consistent with the study of Chalmers *et al.* (1986), who also found no change of plasma ANP after prolonged ACE inhibition. Mann *et al.* (1986) reported a decline of plasma ANP levels after 6 days of enalapril. However, the subjects in that study were on a low sodium diet, which may have resulted in an additional disposition to decreased atrial pressures.

In conclusion, in healthy subjects on a normal sodium intake acute ACE inhibition with cilazaprilat did not change plasma ANP despite clear changes in haemodynamics and in plasma angiotensin II levels. These findings indicate that angiotensin II has little influence on the release of ANP.

We are indebted to Dr P. W. de Leeuw for the determination of angiotensin II levels in his laboratory.

References

- Awah, G. C., Zeigler, D. W. & Kauker, M. L. (1986). Potentiation of the effect of atrial natriuretic factor by captopril in DOCA hypertensive rats. *Fed. Proc.*, **45**, 754.
- Chalmers, J. P., Wing, L. M. H., West, M. J., Bune, A. J. C., Elliott, J. M., Morris, M. J., Cain, M. D., Graham, J. R. & Southgate, D. O. (1986). Effects of enalapril and hydrochlorothiazide on blood pressure, renin-angiotensin system and atrial natriuretic factor in essential hypertension: a double blind factorial cross-over study. *Aust. N.Z. J. Med.*, **16**, 475–480.
- Doorenbos, C. J., Daha, M. R. & van Brummelen, P. (1987). Radioimmunoassay for determination of atrial natriuretic peptide in human plasma. *Pharm. Weekblad [Sci.]*, **9**, 189.
- Gaillard, C. A., Koopmans, H. A. & Dorhout Mees, E. J. (1988). Enalapril attenuates natriuresis of atrial natriuretic factor. *Hypertension*, **11**, 160–165.
- Hansell, P. & Ulfendahl, H. R. (1987). Effects of atrial natriuretic peptide (ANP) during converting enzyme inhibition. *Acta Physiol. Scand.*, **130**, 393–399.
- Higuchi, K., Nawata, H., Kato, K.-I., Ibayashi, H. & Matsuo, H. (1986). Alpha-human atrial natriuretic polypeptide inhibits steroidogenesis in cultured human adrenal cells. *J. clin. Endocrinol. Metab.*, **62**, 941–944.
- Hirata, Y., Ishii, M., Sugimoto, T., Matsuoka, H., Ishimitsu, T., Atarashi, K., Sugimoto, T., Miyata, A., Kangawa, K. & Matsuo, P. (1987). Relationship between the renin-angiotensin system and atrial natriuretic polypeptide in rats. *Clin. Sci.*, **72**, 165–170.
- Hughes, A., Thom, S., Goldberg, P., Martin, G. & Sever, P. (1988). Direct effect of alpha-human atrial natriuretic peptide on human vasculature *in vivo* and *in vitro*. *Clin. Sci.*, **74**, 207–211.
- Iwao, H., Fukui, K., Yamamoto, A., Shoji, T. & Abe, Y. (1987). Effects of captopril on plasma atrial natriuretic polypeptide and the renin angiotensin system in rats. *Clin. exp. Hypertension*, **A9**, 697–701.
- Katz, F. H., Rompf, P. & Smith, J. A. (1975). Diurnal variation of plasma aldosterone, cortisol and renin activity in supine man. *J. clin. Endocrinol. Metab.*, **40**, 125–134.

- Kohno, M., Yasunari, K., Matsuura, T., Kanayama, Y., Takaori, K., Murakawa, K-I. & Takeda, T. (1987). Effect of chronic treatment with angiotensin I converting enzyme inhibitors on circulating atrial natriuretic polypeptide in spontaneously hypertensive rats. *Clin. exp. Hypertension*, **A9**, 693-696.
- Kurtz, A., Della Bruna, R., Pfeilschifter, J., Taugner, R. & Bauer, C. (1986). Atrial natriuretic peptide inhibits renin release from juxtaglomerular cells by a cGMP-mediated process. *Proc. Nat. Acad. Sci. USA*, **83**, 4769-4773.
- Maack, T., Camargo, M. J. F., Kleinert, H. D., Laragh, J. H. & Atlas, S. A. (1985). Atrial natriuretic factor: structure and functional properties. *Kidney Int.*, **27**, 607-615.
- Mann, F. E., Lang, R. E., Leidig, M. & Ritz, E. (1986). Effect of angiotensin I converting enzyme inhibition on circulating atrial natriuretic peptide in humans. *Klin. Wochenschr.*, **64** (Suppl. VI), 13-15.
- Mantero, F., Rocco, S., Pertile, F., Carpena, G., Fallo, F., Leone, L. & Boscaro, M. (1987). Effect of alpha-human atrial natriuretic peptide in low renin essential hypertension and primary aldosteronism. *Clin. exp. Hypertension*, **A9**, 1505-1513.
- McMurray, J. & Struthers, A. D. (1988). Effects of angiotensin II and atrial natriuretic peptide alone and in combination on urinary water and electrolyte excretion in man. *Clin. Sci.*, **74**, 419-425.
- Needleman, P. & Greenwald, J. E. (1986). Atriopeptin: a cardiac hormone intimately involved in fluid, electrolyte, and blood pressure homeostasis. *New Engl. J. Med.*, **314**, 828-834.
- Peuler, J. D. & Johnson, G. A. (1977). Simultaneous single isotope radioenzymatic assay of plasma norepinephrine, epinephrine and dopamine. *Life Sci.*, **21**, 625.
- Solomon, L. R., Atherton, J. C., Bobinski, H. & Green, R. (1986). Effect of posture on plasma immunoreactive atrial natriuretic peptide concentrations in man. *Clin. Sci.*, **71**, 299-300.