Afr. J. Med. med. Sci. (1990) **19**, 33–38.

The cardiovascular and endocrine effects of cilazapril, a new angiotensin-converting enzyme inhibitor, in man

A. A. AJAYI AND J. L. REID*

*Department of Medicine, Obafemi Awolowo University, Ile-Ife, Nigeria and *University Department of Materia Medica, Stobhill General Hospital, Glasgow, U.K.*

Summary

The cardiovascular and renin–angiotensin–aldosterone effects of cilazapril, a new angiotensin-converting enzyme (ACE) inhibitor was evaluated in healthy Caucasians in a double-blind, placebo-controlled, cross-over study. Cilazapril significantly inhibited plasma ACE activity, with a peak inhibition of 82% at 2 h and a residual inhibition of 41% persisting at 24 h. There was a biphasic and significant hypotensive effect, corresponding temporally to plasma ACE inhibition ($P < 0.02$, ANOVA). The hypotensive action was not accompanied by reflex tachycardia. Plasma renin activity rose significantly as a consequence of ACE inhibition ($P < 0.05$, ANOVA) but plasma aldosterone was unaltered. Cilazapril is a potent ACE inhibitor with a rapid onset and prolonged duration of antihypertensive and endocrine effects. Studies of the effects on ACE inhibition on the renin–angiotensin system in Africans are required.

Résumé

L'effet hémodynamique et renine–angiotensin–aldosterone consequénce de cilazapril, un nouveaux inhibiteur du angiotensin convertir enzyme (ACE) a ètè etudie. Cilazapril etaient significativement dimunier plasmatique de la activite du renin, avec maximum inhibiteur de 82% à 2h et residu inhibiteur de 41% a 24 h. Cilazapril etaient significativement dimunier la tension arterielle n'etant simultané pulsation rapide. Les concentrations du plasmatique renin la activite etatient significativement plus hautes ($P < 0.05$, ANOVA). Il ny'a pa de difference notable dans plasmatique aldosterone concentrations. Le recherche l'effet de ACE inhibiteur sur African noir de reniné–angiotensin de besoim.

Correspondence: Dr A. A. Ajayi, Department of Medicine, Faculty of Health Sciences, Obafemi Awolowo University, Ile-Ife, Nigeria.

Introduction

The recent development and clinical availability of angiotensin-converting enzyme (ACE) inhibitors represents a significant landmark in cardiovascular therapy. ACE inhibitors are of proven efficacy in all grades of hypertension, renovascular hypertension and congestive heart failure in Caucasians [1–3]. While there are racially mediated differences in response to ACE inhibitors in hypertensive patients [4], enalapril, a non-thiol long-acting ACE inhibitor, has been shown to improve exercise performance and clinical status in Nigerians with congestive heart failure [5]. Cilazapril (RO-312848) is a newer ACE inhibitor which in animal studies had exhibited greater biochemical and anti-hypertensive potency compared to enalapril [6]. In similar manner to enalapril, cilazapril is converted to cilazaprilat, the active metabolite, following oral administration. The chemical configuration of enalapril, cilazapril and their respective metabolites are shown in Fig. 1. The present study was designed to evaluate the effects of oral cilazapril on the cardiovascular and renin–angiotensin–aldosterone systems in normal man.

Materials and methods

The study was of a placebo-controlled, randomized, double-blind cross-over design, in 10

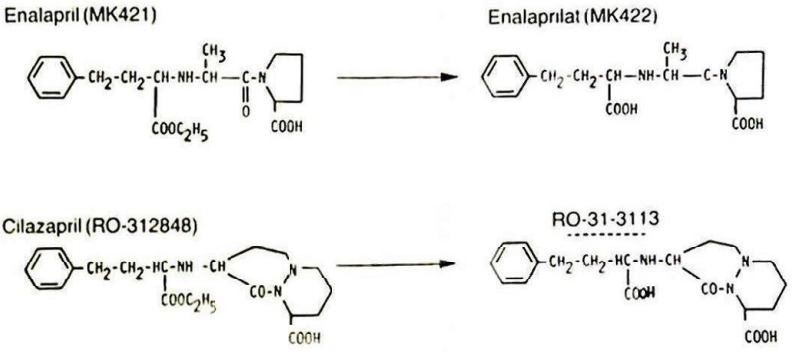

Fig. 1. A comparison of the chemical structures of cilazapril and enalapril and their respective active metabolites cilazaprilat (RO-313113) and enalaprilat (MK 422).

normotensive healthy Caucasian volunteers. The subjects were aged 19–33 years and weighed between 55 and 90 kg. The study was ethically reviewed and approved by the Greater Glassgow Health Board, and all subjects gave informed written consent prior to inclusion in the study. The subjects were judged healthy by history, physical examination, full biochemical and haematological screening, as well as by 12-lead ECGs. All subjects were salt replete as assessed by 24 h urinary Na^+ excretion (154 ± 99 mmol) measured before the study.

On two study days, 2 weeks apart, the volunteers attended the clinical pharmacology research unit at 0830 h, having avoided coffee, alcohol, tea, and cigarettes for 12 h. They were allowed 30 min of supine rest prior to commencement of the study. Cilazapril (10 mg), or a capsule identical in appearance, was administered with 200 ml of water in a random order.

Blood pressure and heart rate were recorded in duplicate after 30 min supine and at 1, 2, 5 min of standing, before and at 1, 2, 3, 4, 6, 8 and 24 h post-dosing. A light snack was allowed after the 2-h recordings. Blood pressure was measured using a semi-automated sphygmomanometer (Sentron Bard Biomedical) and heart rate by precordial ECG electrodes connected to a Gross polygraph recorder model 7D1D (Grass Instruments Co., Massachusetts, U.S.A.). Blood samples for plasma ACE activity were collected at the same times as the blood pressure recording. Additional samples for plasma renin activity (PRA) and plasma aldosterone (PA) were obtained at 0, 2, 4, 8, and 24 h after dosing. ACE activity was measured by the method of Cushman and Cheung [7] as modified by Chiknas [8]. The inter- and intra-assay coefficients of variation were 6 and 2%, respectively, and the limit of detection was 0.1 units.

Plasma renin activity was assayed by the method of Derkx *et al.* [9]. The normal range in our laboratory was 4–12 ng AI/ml/h and the detection limit 1 ng AI/ml/h, inter- and intra-assay variability being 7.0 and 5.5% respectively. Plasma aldosterone was measured by radioimmunoassay [10], the inter- and intra-assay variation being 11 and 7%, with a detection limit of 10 pg/ml.

Percentage ACE inhibition was calculated as:

$$\frac{\text{baseline ACE activity} - \text{observed ACE activity}}{\text{baseline ACE activity}} \times 100.$$

All results are expressed as mean ± s.d. (Eu/ml), where 1 Eu generates 1 nmol hippuric acid per minute. The blood pressure, heart rate and endocrine responses were subjected to repeated measures analysis of variance (ANOVA). The null hypothesis was rejected if $P < 0.05$.

Results

No biochemical or haematological abnormality was found following routine testing after cilazapril. Three subjects, however, experienced mild but transient postural dizziness on cilazapril.

Effects on blood pressure and heart rate

The cardiovascular response to cilazapril is shown in Fig. 2. There was a significant reduction ($P < 0.02$, ANOVA) in both systolic and diastolic blood pressure, in the supine and erect posture. This hypotensive effect was not associated with a reflex tachycardia in either posture (Fig. 2). The antihypertensive action of cilazapril was apparent within 2 h of dosing, maximal at 6–8 h, but no discernible effect was present at 24 h.

Effects on the renin–angiotensin–aldosterone axis

Following cilazapril, plasma ACE activity was significantly inhibited within 1 h, and a peak ACE inhibition of 82.2 ± 12.5% was attained at 2 h. At 24 h, the residual inhibition was significant and persisted at 41.6 ± 20.0% (Fig. 3).

Following converting-enzyme inhibition, plasma renin activity was significantly elevated ($P < 0.05$, ANOVA). This rise was apparent within 2 h of cilazapril, with a peak at 4 h.

The peak PRA increase was coincident with the maximal hypotensive action (Fig. 4). Plasma aldosterone was not significantly reduced relative to placebo, following cilazapril administration in the present study (Fig. 4).

Discussion

In this double-blind study, the ACE inhibitor, cilazapril caused a significant and long-lasting inhibition of the renin–angiotensin–aldosterone axis and a prolonged hypotensive action. These observations are consistent with in-vivo and in-vitro animal data [6] and preliminary human experience [11]. The peak ACE inhibition occurred early at 2 h, despite the need to absorb and de-esterify cilazapril to its active metabolite, cilazaprilat. This contrasts with the peak ACE inhibition, after enalapril, which occurs after 4 h [12] and suggests a more rapid onset of action of cilazapril compared to enalapril

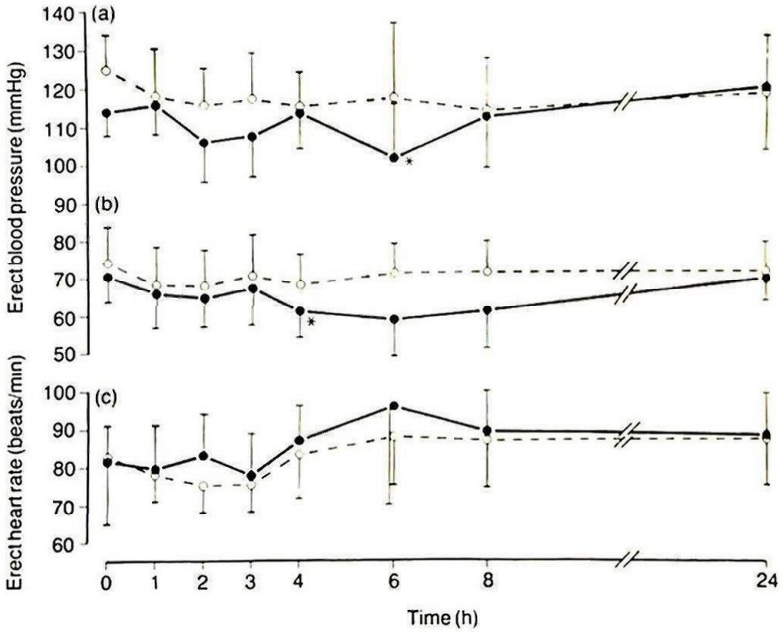

Fig. 2. The effect of cilazapril on erect systolic (a) and diastolic (b) blood pressure and heart rate (c). *Cilazapril significantly reduced blood pressure ($P < 0.02$, ANOVA) without tachycardia ($n = 10$). Values represent means ± s.d.

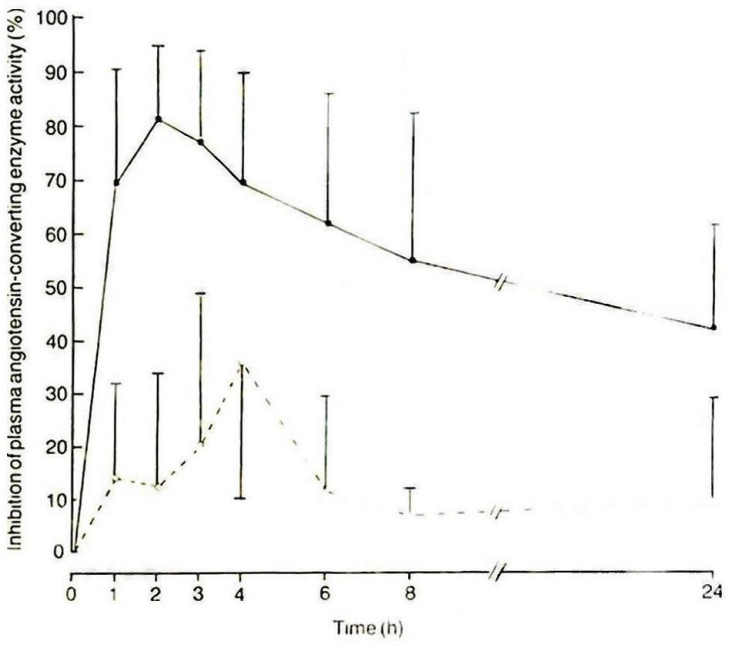

Fig. 3. Inhibition of plasma ACE activity by cilazapril (■) ($n = 10$). Values represent means ± s.d

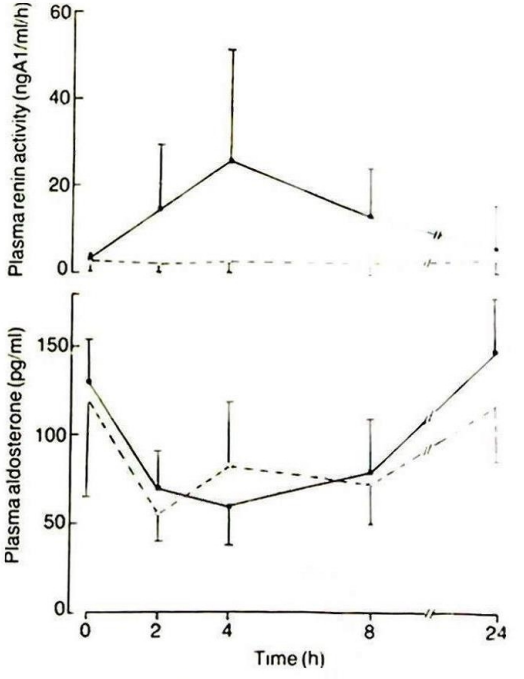

Fig. 4. The influence of cilazapril (■) and placebo (○) on plasma renin activity and plasma aldosterone in salt-replete normal volunteers. Cilazapril significantly increased plasma renin activity relative to placebo ($P < 0.05$, ANOVA).

in normal men. Residual ACE inhibition was still significant at 24 h, suggesting that single daily dosing would be adequate. There was a temporal correspondence between ACE inhibition in plasma and the antihypertensive action. The blood pressure fall, however, appeared biphasic, with an initial reduction in systolic BP at 2 h and a greater fall at 6 h. This biphasic hypotensive action has also been seen after enalapril [12], and may be related to differential inhibition of plasma and vascular wall ACE activity [13]. The fall in blood pressure following cilazapril was not associated with a reflex tachycardia that would normally accompany arterial vasodilation. This absence of reflex cardio-stimulation with hypotension appears to be a general property of ACE inhibitors, which at least in part, is due to an enhancement of cardiac parasympathetic activity [14,15] following release of vagal efferents from angiotensin II-mediated inhibition [16].

Plasma renin activity was significantly increased within 1 h of cilazapril, with a peak at 4 h. The increment in PRA following ACE inhibition results from the removal of the negative feedback control of angiotensin II on renin secretion, as well as the activation of the renal baroreceptor mechanisms following BP fall. Plasma aldosterone was not suppressed by cilazapril in the present study. The effect of ACE inhibitors on aldosterone has been variable [11,12] and this may reflect the degree of reduction in circulating angiotensin II induced by converting-enzyme inhibition.

Thus, cilazapril is a potent inhibitor of ACE and significantly reduced blood pressure in salt-replete normal Caucasian subjects. It had a rapid onset and a prolonged duration of cardiovascular and endocrine effects. As the basal PRA is known to differ between blacks and whites [17] and as this affects the antihypertensive efficacy [4], further study of effects on ACE inhibitors on the renin–angiotensin system in Africans is warranted.

Acknowledgments

We are grateful to Jim McCulloch and David Hughes for excellent technical help. We thank Mrs F. M. Adesida for typing the manuscript.

References

1. Gavras H, Brunner HR, Scaley JE, Gavras I, Vucovich RA. An angiotensin converting enzyme inhibitor to identify and treat vasoconstrictor and volume factors in hypertensive patients. N Engl J Med 1974;291:817–21.
2. Hodsman GP, Brown JJ, Davies DC *et al.* Converting enzyme inhibitor, enalapril, in the treatment of hypertension with renal artery stenosis. Br Med J 1982;285:1697–9.
3. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. N Engl J Med 1987;316:1429–35.
4. Ajayi AA, Ladipo GOA, Oyewo EA, Akinsola A. Enalapril and hydrochlorothiazide in hypertensive Africans. Eur J Clin Pharmacol 1989;36: 229–34.
5. Ajayi AA, Balogun MO, Oyewo EA, Ladipo GOA. Enalapril in African patients with congestive cardiac failure. Br J Clin Pharmacol 1989;27:400–3.
6. Natoff IL, Nixon JS, Francis RJ *et al.* Biological properties of the angiotensin converting enzyme inhibitor Cilazapril. J Cardiovasc Pharmacol 1985;7:569–80.
7. Cushman DW, Cheung HS. Spectrophotometric assay and properties of angiotensin converting enzyme in rabbit lung. Biochem Pharmacol 1971;20:1637–95.
8. Chiknas SG. A liquid chromatography assisted assay for converting enzyme (peptidyl dipeptidase) in plasma. Clin Chem 1979;25:1259–62.
9. Derkx FHM, Wenting GJ, Man'nt veid AJ, Verhoeven RP, Schalc Kamp MADH. Control of enzymatically inactive renin in man under various pathological conditions. Implications for the interpretations of renin measurements in peripheral venous plasma. Clin Sci Mol Med 1978;54:529–38.
10. McKenzie JK, Clements JA. Simplified radioimmunoassay for serum aldosterone utilising increased antibody specificity. Clin Endocrinol Metab 1974;38:622–7.
11. Ajayi AA, Elliot HL, Reid JL. Pharmacodynamics and dose–response relationships of angiotensin converting enzyme, cilazapril, in essential hypertension. Br J Clin Pharmacol 1986;22:167–76.
12. Ajayi AA, Hockings N, Reid JL. Age and the pharmacodynamics of angiotensin converting enzyme inhibitors, enalapril and enalaprilat. Br J Clin Pharmacol 1986;21:349–57.
13. Dzau VJ. Vascular renin–angiotensin. A possible autocrine or paracrine system in control of vascular function. J Cardiovasc Pharmacol 1984;6:S377–82.
14. Sturani A, Chiarini C, Degli Esposti E, Santoro A, Zuccala A, Zuchelli P. Heart rate control in hypertensive patients treated by Captopril. Br J Clin Pharmacol 1982;14:849–55.
15. Ajayi AA, Campbell BC, Howie CA, Reid JL. Acute and chronic effects of converting enzyme

inhibitors on the reflex control of heart rate in normotensive man. J Hypertension 1985;3:47–53.

16. Lumbers ER, McCloskey DI, Potter EK. Inhibition by angiotensin II of baroreceptor evoked activity in cardiac vagal efferents in the dog. J Physiol 1979;294:69–80.

17. Osotimehin B, Erasmus RT, Iyun AO, Falase AO, Ahmad Z. Plasma renin activity and plasma aldosterone concentration in untreated Nigerians with essential hypertension. Afr J Med Med Sci 1984;13:139–43.

(*Accepted* 27 *September* 1988)