Hormonal and Metabolic Effects of Enalapril Treatment in Hypertensive Subjects With NIDDM

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The effects of enalapril treatment on blood glucose, insulin, and C-peptide levels and effects on the renin-angiotensin aldosterone system were studied in 22 hypertensive patients with non-insulin-dependent diabetes. After a 4-wk run-in period during which all previous antihypertensive drugs were discontinued, treatment was commenced with one daily dose of 10 mg enalapril. The dose was adjusted upward at 3-wk intervals to a maximum of 40 mg daily. In 3 subjects, addition of a thiazide diuretic was required after 9 wk of treatment. At completion of run-in and after 9 and 13 wk of treatment, subjects had blood samples drawn after fasting and 2 h after a standardized 1.6-mJ mixed meal. Mean fasting blood glucose at the end of the run-in period was 8.3 ± 0.5 mM and at study completion was 7.3 ± 0.4 mM. Mean postprandial blood glucose was 10.8 ± 1.0 mM before treatment and 9.8 ± 0.7 mM at study completion. The changes in fasting and postprandial blood glucose levels were not significant ($P = .06$ and $P = .15$, respectively). There was no significant change in glycosylated hemoglobin levels. Fasting and meal-stimulated insulin and C-peptide levels were not altered by enalapril treatment. Treatment was associated with a sustained reduction in plasma angiotensin-converting enzyme activity, an increase in plasma renin activity, reduced plasma aldosterone levels, and significant reductions in supine, seated, and standing arterial blood pressures. There was a small rise in mean plasma potassium from 4.0 ± 0.09 to 4.2 ± 0.09 mM after 3 wk of treatment, but after 9 wk, potassium levels had returned to pretreatment levels. Plasma creatinine levels did not change. *Diabetes Care* 11:397–401, 1988

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Arterial hypertension is a common problem in patients with diabetes mellitus and is associated with an increased incidence of both microvascular and macrovascular complications (1). The standard first-line antihypertensive drugs have traditionally been diuretics and β-blockers (1). Thiazide diuretics have well-documented effects in inducing hyperglycemia partly as a consequence of hypokalemia, although potassium-sparing diuretics can also have a diabetogenic effect (2). β-blockers, particularly those that are not cardioselective, may also be mildly diabetogenic and can impair physiologic responses to hypoglycemia (2). Both groups of drugs can have potentially adverse effects on the blood lipid profile (3), which is particularly undesirable in patients with diabetes, who as a group are predisposed to vascular disease (4).

Angiotensin-converting enzyme (ACE) inhibitors present a potential alternative form of therapy, because they would not be expected to interfere with diabetes control, the response to hypoglycemia, or the blood lipid profile. Despite reports that hypertension in patients with diabetes is associated with suppression of the renin-angiotensin aldosterone system (5), small clinical studies with captopril (6,7) and enalapril (8) have shown ACE inhibitors to be effective therapy without significant adverse effects. A beneficial effect on diabetic nephropathy with reduced albuminuria but maintained glomerular filtration rate has been demonstrated in hypertensive (9,10) and normotensive (11) subjects.

There have been anecdotal reports of blood glucose–lowering effects of captopril (12,13), and in a controlled trial, enalapril treatment was associated with a small but significant reduction in fasting blood glucose in nondiabetic individuals as opposed to atenolol, which caused a small rise (14). In this study, we assess the effects of enalapril on blood glucose, insulin, and C-peptide levels, and on the renin-angiotensin aldosterone system in

hypertensive subjects with non-insulin-dependent diabetes mellitus (NIDDM).

MATERIALS AND METHODS

Patients being treated for NIDDM who were also hypertensive or were receiving antihypertensive medication were identified in diabetes clinics and general practices. The study protocol was approved by the Canterbury Hospital Board's ethical committee. Patients entering this study attended a special outpatient clinic. At the initial visit, written informed consent was obtained, and a history and physical examination were undertaken. Baseline chest X-ray, ECG, biochemistry, and hematology screens were performed. Glycosylated hemoglobin (GHb) was measured. All antihypertensive medication was withdrawn, this being achieved over a 1-wk period if the patient was on a β-blocker and immediately if not. Therapy for diabetes was not altered. The patients were seen again at 2 wk, and then at 4 wk off previous antihypertensive treatment, at which stage, treatment with 10 mg enalapril/day was commenced if the diastolic blood pressure was >95 mmHg or if the systolic blood pressure was >160 mmHg. If at the 2-wk visit the blood pressure was unduly elevated (diastolic blood pressure >110 mmHg), the patient entered the treatment phase at that stage. Enalapril was administered once daily at 0800 h throughout the treatment period.

At the end of the run-in period (wk 4), blood was taken with the patient fasting. Patients then consumed a standardized 1.6-mJ mixed meal, and further blood samples were drawn 2 h later, after the patient was quietly ambulant for at least 0.5 h before sampling. Blood glucose, insulin, and C-peptide levels were measured on the fasting sample. On the 2-h postmeal sample, biochemistry screen, blood glucose, insulin, C-peptide, plasma renin activity (PRA), ACE activity, cortisol, and aldosterone levels were measured. Blood glucose was measured by the glucose oxidase method. Biochemistry screens were performed on the Technicon SMAC system. Insulin was measured by radioimmunoassay (RIA) based on the method of Albano et al. (15). Human insulin (Novo, Copenhagen) was used for standards and tracer. Charcoal was used as the separation procedure. C-peptide was measured by RIA (antiserum M1230) with the method of Heding and Rasmussen (16). Synthetic human C-peptide (Novo) was used for standards, and ^{125}I-labeled synthetic human tyrosine–C-peptide was used as tracer. GHb was measured by automated fluorometric determination of hydroxymethylfurfural (HMF) in acid-treated hemolysates of red blood cells (17) and was expressed as micromoles of HMF per gram hemoglobin (normal nondiabetic range 1.8–2.6 μM HMF/g Hb). PRA was measured by RIA of generated angiotensin I after 3 h of incubation at pH 7.4 (18). Aldosterone was measured by direct RIA (19). ACE activity was measured with hippuryl-L-histidyl-L-leucine as substrate (19). Cortisol was measured by an enzyme-linked immunosorbent assay (ELISA; 20).

Patients were seen after 3 wk on 10 mg enalapril daily (wk 7), and if blood pressure control was satisfactory with a diastolic blood pressure of <90 mmHg and a systolic blood pressure of <160 mmHg, the dose was continued unchanged. If the blood pressure was above these levels, the dose was increased to 20 mg daily. The patients were seen again 3 wk later (wk 10), and the dose was adjusted if necessary up to 40 mg daily with the same criteria. A biochemistry screen was performed at each clinic visit. After a further 3 wk (wk 13), the mixed-meal test was repeated with fasting and 2-h blood samples. If blood pressure was not within the target range, 0.25 mg cyclopenthiazide daily was added to the treatment regimen. All patients were seen 4 wk later (wk 17) and had the mixed-meal test and blood sampling performed again.

All blood pressure measurements were carried out by one observer with a London School of Hygiene sphygmomanometer (Rose box). Measurements were made at the same time of day under identical conditions at each visit. The fifth Korotkoff sounds were taken as the diastolic pressure. One supine and three seated blood pressure readings were taken. A further reading was taken immediately after standing. All treatment decisions were based on the seated blood pressure. The seated blood pressure was recorded as the mean of the second two seated blood pressure readings.

Statistical analyses were undertaken with the hypothesis tests for means (Student's *t* test) and regression analysis with the Microstat statistics package on an IBM personal computer. Results are given as means ± SE.

Subjects. Thirty-two patients with NIDDM entered the study. Ten were dropped from the study at the end of the run-in period because their arterial blood pressures were <160/95 mmHg. The remaining 22 patients completed the study period, except for 1 who, before the final visit, was admitted to the hospital with an ischemic leg requiring amputation. Results for this patient are included in all the analyses except for wk 17 (final visit). The 22 patients entering the treatment period were 41–75 yr of age. Seventeen of them were on other antihypertensive drugs before entering the study, and these drugs included diuretics for 9. Twelve patients were on oral hypoglycemic agents, and 10 were on diet therapy only. Their diabetes treatment was not altered during the study.

RESULTS

Mean fasting blood glucose at the end of the run-in period was 8.3 ± 0.5 mM and at wk 13 and 17, 8.1 ± 0.5 and 7.3 ± 0.4 mM, respectively. Mean postprandial blood glucose at the end of the run-in period was 10.8 ± 1.0 mM and at wk 13 and 17, 9.6 ± 0.8 and 9.8 ± 0.7 mM (Table 1). The mean change in fasting

TABLE 1
Pretreatment and posttreatment clinical characteristics of study subjects

		Week					
		0	4	7	10	13	17
Fasting glucose	(mM)		8.3 ± 0.5			8.1 ± 0.5	7.3 ± 0.4
2-h postmeal glucose	(mM)		10.8 ± 1.0			9.6 ± 0.8	9.8 ± 0.7
Fasting insulin	(mU/L)		13.5 ± 2.0			14.4 ± 1.6	13.9 ± 1.8
2-h postmeal insulin	(mU/L)		53.3 ± 8.0			64.3 ± 10.5	58.0 ± 10.1
Fasting C-peptide	(pM)		786 ± 57			855 ± 55	801 ± 65
2-h postmeal C-peptide	(pM)		2102 ± 189			2233 ± 223	2213 ± 255
Aldosterone	(pM)		170.3 ± 18.6			123.8 ± 2.9*	118.7 ± 13.7†
Potassium	(mM)	3.9 ± 0.08	4.0 ± 0.09	4.2 ± 0.07‡	4.0 ± 0.07	4.0 ± 0.07	4.0 ± 0.07
Creatinine	(mM)	0.09 ± 0.004	0.09 ± 0.003	0.09 ± 0.002	0.09 ± 0.004	0.09 ± 0.003	0.09 ± 0.003
Cortisol	(nM)		311.7 ± 25.1			300.8 ± 24.2	274.2 ± 23.1

Values are means ± SE.
Significance of change from pretreatment (wk 4) *$P < .002$, †$P < .001$, ‡$P = .02$.

blood glucose of −0.9 ± 0.6 mM was not statistically significant ($P = .06$) and neither was the change in postprandial blood glucose of −0.7 ± 0.7 ($P = .15$) at wk 17. Mean GHb at entry to the study was 2.99 ± 0.11 μmol HMF/g Hb and at wk 17, 2.84 ± 0.11 μmol HMF/g Hb. The change was not significant ($P = .16$). There were no significant changes in either fasting or meal-stimulated insulin levels, and similarly there were no significant changes in C-peptide levels (Table 1). There was no change in plasma sodium or creatinine levels during the study period. A small rise in mean plasma potassium occurred during the run-in period from 3.9 ± 0.08 to 4.0 ± 0.09 mM (NS). After 3 wk of treatment with enalapril, the mean potassium level was 4.2 ± 0.09 mM, a mean change of +0.2 mM, which was statistically significant ($P = .02$). After completion of the 9-wk treatment period, however, the mean potassium level was unchanged from the pretreatment level at 4.0 ± 0.07 mM. The maximum potassium level observed during the whole study period was 5.2 mM, and at study completion no patient had a potassium level >5.0 mM.

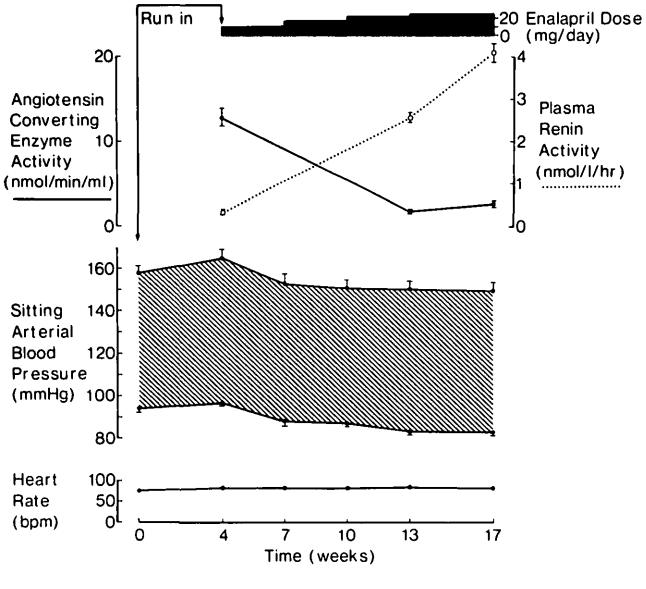

FIG. 1. Blood pressure, heart rate, and changes in angiotensin-converting enzyme activity and plasma renin activity during 17-wk study.

As expected, there was a marked reduction in plasma ACE activity by wk 13 ($P = 3 \times 10^{-8}$) but no change thereafter (Fig. 1). Also as expected, there was an eightfold increase in PRA by wk 13 ($P = .02$) with an additional rise by wk 17 ($P = .06$; Fig. 1). It was apparent from the data that two patients at wk 17 were not taking the medication as prescribed, because their ACE levels had returned to pretreatment levels; but their data have been included in all analyses. There was a significant fall in plasma aldosterone level on treatment, which was evident at 13 wk and sustained at 17 wk (Table 1, $P < .001$).

There was a slight rise in seated blood pressure during the run-in period, which was not statistically significant (Fig. 1). After 3 wk on 10 mg/day enalapril, seated blood pressure was significantly reduced ($P < .001$), and at wk 17 remained significantly lower than both blood pressure at the end of the run-in period ($P < .001$) and entry blood pressure ($P < .03$). Similar changes in supine and standing blood pressure levels were observed (Table 2). Three subjects required addition of 0.25 mg cyclopenthiazide per day for antihypertensive treatment at wk 13. Heart rate increased during the run-in phase by a mean of 4.0 ± 3.5 beats/min (NS). There was no change in heart rate on treatment (Fig. 1). There was no significant correlation between the response to blood pressure treatment and baseline PRA, nor was the change in PRA significantly correlated with the change in blood pressure. There was a significant correlation between the fall in aldosterone level and the fall in diastolic blood pressure ($r = .45$, $P = .03$) but not systolic blood pres-

TABLE 2
Supine and standing blood pressure and weight

	Week					
	0	4	7	10	13	17
Mean dose enalapril (mg/day)		0	10	15.9	23.6	25.2*
Supine blood pressure (mmHg)						
Systolic	165.6 ± 4.5	162.7 ± 3.7	153.6 ± 3.8†	151.3 ± 3.9‡	149.5 ± 4.6§	148.1 ± 4.1‡
Diastolic	91.7 ± 1.7	89.3 ± 2.3	83.6 ± 2.5§	83.7 ± 2.3§	80.4 ± 1.9§	81.2 ± 2.1‡
Standing blood pressure (mmHg)						
Systolic	154.3 ± 5.7	164.8 ± 3.8	151.2 ± 4.2‡	148.9 ± 4.2‡	148.1 ± 4.5‡	148.5 ± 4.1‡
Diastolic	91.7 ± 1.9	97.5 ± 1.5	88.5 ± 2.5§	87.2 ± 1.5‡	83.4 ± 1.6‡	84.4 ± 1.9‡‖
Weight (kg)	72.4 ± 2.2	72.5 ± 2.2‖	71.8 ± 2.1§‖	70.8 ± 2.1‡	70.4 ± 2.1‡	69.9 ± 2.3‡‖

Values are means ± SE.
*Enalapril plus diuretic in 3 cases.
Significance of change from pretreatment (wk 4) †$P < .02$, ‡$P < .001$, §$P < .01$.
‖Data on one case missing.

sure ($r = .32$, $P = .15$) at wk 13. At wk 17, the correlations between change in blood pressure and change in aldosterone levels were not statistically significant ($r = .21$ for systolic and $r = .35$ for diastolic blood pressure).

No patient was withdrawn during the study period because of side effects. Three patients experienced transient postural dizziness. One patient complained of a persistent cough during the study period, and both this patient and another patient discontinued enalapril beyond the 17-wk study period for this reason.

DISCUSSION

Enalapril treatment was not associated with any change in diabetes control. The slight reduction in blood glucose levels on treatment was not significant. Anecdotal reports of blood glucose–lowering effects of ACE inhibitors in subjects with diabetes have appeared (12,13) but have not been confirmed by other experience (8,21,22). However, in a study of nondiabetic hypertensive subjects, treatment with enalapril for a 26-wk period was associated with a fall in mean fasting blood glucose from 5.0 to 4.7 mM, a change that was significant (14). The small number of subjects in our study would make detection of such minor changes in blood glucose levels unlikely. There is no obvious mechanism by which ACE inhibitors would be expected to influence blood glucose levels. We have found both fasting and meal-stimulated insulin and C-peptide levels to be unaltered by treatment with enalapril. Because only three subjects required addition of a diuretic, it was not possible to assess the effect on glucose tolerance of combined ACE inhibitor and diuretic treatment. Although the study design may have failed to detect some subtle effect on carbohydrate metabolism, enalapril appears to have no clinically important impact on diabetes control.

The effects of enalapril in decreasing plasma ACE activity, increasing PRA, and reducing plasma aldosterone were predictable, and there was no loss of effect during the study period. The slight increase in plasma potassium early in treatment was minor, and no patient developed significant hyperkalemia. Plasma creatinine levels were not altered by enalapril treatment. Although no control group was studied, the slight rise in blood pressure during the run-in period after withdrawal of other antihypertensive agents, and the prompt drop in blood pressure on introduction of enalapril, suggest that the treatment was responsible for the statistically significant reduction that was observed in blood pressure. With the lack of a control group, it was not possible to determine whether the small but significant fall in body weight during the study period reflected increased attention to diet or the reduced aldosterone levels on treatment, resulting in a reduction in total body sodium (23). The only significant side effect was the development of a dry persistent cough, a well-recognized side effect of treatment with ACE inhibitors (24); two patients discontinued the drug at longer term follow-up because of persistent cough.

Enalapril administered to subjects with NIDDM produces the expected changes in the renin-angiotensin aldosterone system but no change in insulin secretion or blood glucose levels.

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