Effects of Enalapril in Insulin-Dependent Diabetic Subjects With Mild to Moderate Uncomplicated Hypertension

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The antihypertensive efficacy of enalapril and its effects on the metabolism and kidney function were investigated in 11 insulin-dependent diabetic subjects with uncomplicated mild to moderate hypertension. During a short-term single-blind controlled trial, one daily dose of 20 or 40 mg enalapril significantly reduced both systolic and diastolic blood pressure. In the supine position, mean systolic blood pressure declined from 169 ± 6 to 142 ± 6 mmHg ($P < .01$) and mean diastolic blood pressure from 101 ± 1.5 to 85 ± 2 mmHg ($P < .001$). No changes in heart rate or postural hypotension were observed.

During 1 yr of treatment, the antihypertensive efficacy of enalapril did not decline, and no clinical side effects were observed. Inhibition by enalapril of angiotensin-converting enzyme did not modify daily insulin requirements, glycemic control, uricemia, or lipid metabolism; kalemia and the markers of diabetic nephropathy were not significantly altered. These results suggest that enalapril once daily should be used as the first step in the treatment of diabetic patients with mild to moderate hypertension.
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The use of available antihypertensive drugs is limited by the relatively high incidence of their clinical or biological side effects (1) and their relative lack of efficacy (2). In diabetic subjects the prevalence of hypertension is high: at least 30% of the diabetic population qualifies for antihypertensive treatment (3). Diabetic hypertensives are particularly prone to suffer side effects from antihypertensive therapy (4), and it is therefore expected that new therapeutic agents such as converting enzyme inhibitors will be more efficacious and have fewer side effects. Enalapril, a new long-acting converting enzyme inhibitor, blocks the conversion of angiotensin I into angiotensin II, the active hormone of the renin-angiotensin system. This inhibition leads to a reduction in angiotensin vasoconstriction, bradykinin degradation, and aldosterone production (5). In double-blind controlled trials, administration of enalapril in a dose up to 40 mg once daily proved to be as effective as 80 mg propranolol, 100 mg atenolol, or 50 mg hydrochlorothiazide twice daily (6). The effects of long-term administration of enalapril in insulin-dependent diabetic hypertensives have never been reported. The aim of our study was therefore to investigate the antihypertensive efficacy and the metabolic and renal consequences of enalapril in such patients with mild to moderate uncomplicated hypertension.

SUBJECTS AND METHODS

Subjects. Informed consent was given by all subjects studied. Fifteen Caucasians were selected according to the following criteria: *1*) insulin-dependent diabetic subjects, using National Diabetes Data Group criteria; *2*) diastolic blood pressure (DBP) of 90–115 mmHg (mean of 3 outpatient determinations), on a moderate salt-restricted diet; *3*) no antihypertensive treatment for at least 6 wk before the trial; *4*) no medication other than insulin; *5*) absence of cardiovascular complications on clinical examination and electrocardiogram at rest, and no macroproteinuria (Albustix positive); 6) no evidence of secondary hypertension, after clinical examination, serum electrolytes and creatinine, urinary catecholamines determination and if necessary intravenous pyelography.

Three patients had increased urinary albumin excretion rate (microalbuminuria), suggesting incipient diabetic nephropathy. Four patients were excluded after the initial 2 wk on placebo because their DBP fell to <90 mmHg. The 11

TABLE 1
Short-term trial: main individual clinical characteristics

Patient	Sex	Age (yr)	Duration of diabetes (yr)	Body mass index (kg/m^2)	Diastolic blood pressure (mmHg)	Systolic blood pressure (mmHg)
G.E.	M	58	14	22.75	104	164
D.Re.	F	50	30	21.09	95	174
M.A.	F	28	26	19.63	96	150
D.Ro.	M	65	20	24.10	112	178
R.J.	M	54	20	25.73	103	156
B.H.	F	64	17	25.23	105	218
D.J.	M	50	36	23.46	97	155
D.L.	M	56	16	24.87	105	169
R.R.	M	66	26	24.39	100	189
H.J.	M	48	19	23.39	95	161
A.N.	M	47	27	25.01	100	144

patients included in the trial (8 men, 3 women) had a mean age of 53 ± 3.1 yr (range 28–66), mean body mass index of 23.6 ± 0.5 kg/m^2 (range 19.6–25.7), and mean duration of diabetes of 22.8 ± 1.9 yr (range 14–36). Individual main clinical data are given in Table 1.

Design of the trial and methods. The trial was divided into two parts. The first consisted of a short-term single-blind trial with two placebo periods, and the second was an open 1-yr trial.

In the first part, subjects (N = 15) were given a placebo at 0800 h for 2 wk. The 11 subjects whose supine DBP remained >90 mmHg were then given 20 mg enalapril once daily, and the other four were excluded. For the 6 subjects whose supine DBP was still >90 mmHg 6 wk later, the dose of enalapril was increased to 40 mg once daily. The other 5 continued with 20 mg daily. After 12 wk on enalapril treatment, a placebo (1 or 2 pills) was introduced for a second 2-wk period. Subjects visited the outpatient clinic at 0, 8, and 16 wk and were hospitalized at 2 and 14 wk, i.e., before and during treatment with enalapril. Heart rate and supine and upright blood pressure were recorded by the same observer (H.L.) between 1000 and 1100 h. Blood pressure was measured with a mercury sphygmomanometer, and the point of disappearance of the fifth Korotkoff sound was taken as the DBP. Mean arterial blood pressure was calculated as DBP plus one-third of pulse pressure.

Capillary blood glucose was measured 2–4 times/day throughout the trial according to patient's compliance; most of the determinations were made during fasting with a meter (Glucometer, Ames, Elkhart, IN). The results were noted in a daily book, which also included any clinical hypoglycemic episodes and the daily insulin requirements. During each outpatient visit, potassium, creatinine, and uric acid were determined by conventional methods. Glycemic control was estimated by postprandial plasma glucose (2 h after the meal) with the glucose oxidase method adapted to an autoanalyzer, and total glycosylated hemoglobin (HbA_1) was determined with microcolumn chromatography (kit Cordis, upper limit of normal values <7%). During hospitalizations, the same parameters were measured, as well as fasting plasma glucose, 24-h glycosuria, triglycerides, total cholesterol, HDL cholesterol (enzymatic methods), creatinine clearance, urinary kallikrein (kininogenase activity) (7), 24-h urinary albumin excretion (radioimmunoassay) (8), and β_2-microglobulinuria (9). Plasma renin activity was measured by angiotensin I radioimmunoassay (10). For the last five

TABLE 2
Short-term trial: normal values in 30 controls and values for parameters used to monitor renal function under placebo and enalapril

	Controls	Placebo (H_1)	Enalapril (H_2)
Kalemia (mM)	4.1 ± 0.2	4.3 ± 0.2	4.3 ± 0.1
Natriuresis (mmol/24 h)	150 ± 22	105 ± 14	137 ± 11
Creatinine clearance (ml/min)	93 ± 4	70 ± 11	68 ± 8
Albumin excretion rate (mg/24 h)	6.9 ± 0.8	46.6 ± 33.6	23.5 ± 14.5
Urinary β_2-microglobulin (μg/24 h)	118 ± 29	200 ± 61	111 ± 27
Urinary kallikrein (μg LBK/min)	86 ± 9	13 ± 3	14 ± 4
Plasma renin activity (ng AI · min^{-1} · ml^{-1})			
Supine	5–30	17.4 ± 4.3	76.7 ± 17.5
Upright	15–50	38.9 ± 13.1	206.7 ± 47.6

H_1, H_2: hospitalization periods 1 and 2. LBK, lysylbradykinin; AI, angiotensin I.

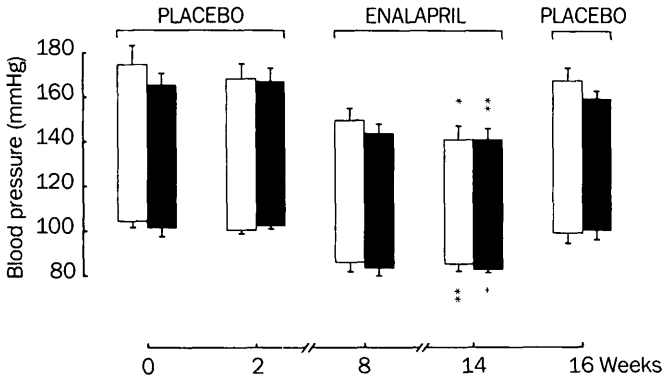

FIG. 1. Short-term trial (N = 11). Comparison of mean blood pressure at wk 2 and wk 14 in supine (*open bar*) and upright (*shaded bar*) positions. Statistically significant differences: *P < .01 for SBP in supine position, **P < .001 for DBP in supine position and for SBP and DBP in upright position.

determinations and for potassium and natriuresis, normal values in 30 controls (normotensive nondiabetic subjects) are given in Table 2.

In the second part of the trial, patients were referred to their usual diabetologist or general practitioner for 1 yr. They were instructed to maintain the same dose of enalapril as they were taking at the end of the short-term trial. After 1 yr of treatment, 10 subjects were hospitalized for measurement of the same parameters as those recorded during the two previous hospitalization periods. One patient was not in the follow-up because he moved out of France.

Throughout the trial during outpatient visits and hospitalizations, clinical side effects of enalapril were checked by questionnaire.

Statistical methods. Results are expressed as means ± SE. Statistical analysis was performed after analysis of variance with Student's t test for unpaired values and Wilcoxon's rank-sum test for paired values. $P < .05$ was considered statistically significant.

RESULTS

Short-Term Trial

Antihypertensive efficacy of enalapril. Before treatment, mean arterial blood pressure was 124 ± 2.6 mmHg; with enalapril it fell to 105 ± 3.5 mmHg ($P < .001$) but rose during the second placebo period to 120 ± 4 mmHg ($P < .01$). Supine and upright systolic blood pressure (SBP) and DBP are shown in Fig. 1. Before enalapril, mean supine SBP was 169 ± 6 mmHg and mean supine DBP was 101 ± 1.5 mmHg, compared with 142 ± 6 and 85 ± 2 mmHg, respectively, under enalapril. The differences were statistically significant: $P < .01$ and $P < .001$, respectively. In 6 of the 11 patients, blood pressures fell to <140 and 90 mmHg in the supine and upright positions. No postural hypotension was observed nor were any significant variations in heart rate.

Effects of enalapril on the metabolism. Daily insulin requirements and the results of the determinations used to assess glycemic control, uric acid, and lipid metabolism are shown in Table 3. During placebo and enalapril treatment, the results were very similar and no significant difference was found nor was any unusual or severe hypoglycemic episode observed throughout the trial.

Effects of enalapril on kidney function. Kalemia and creatinine clearance were not modified by enalapril. The reductions in β_2-microglobulinuria and the urinary albumin excretion rate did not reach statistical significance. Urinary kallikrein activity significantly reduced in these diabetic patients was not further modified by enalapril. As expected, basal values for plasma renin activity rose under enalapril by 566 ± 207%. The results of the determinations used to monitor renal function are shown in Table 2.

Long-Term Trial

Antihypertensive efficacy. After 1 yr of treatment, mean supine SBP was 137 ± 8 mmHg and mean supine DBP 82 ± 3 mmHg; compared with pretreatment values, the differences were statistically significant ($P < .01$ and $P < .001$, respectively). The antihypertensive efficacy of enalapril did not

TABLE 3
Short-term trial: metabolic control under placebo and enalapril

	Placebo		Enalapril		
	V_1	H_1	V_2	H_2	Placebo (V_3)
Fasting plasma glucose (mM)	6.2 ± 0.7	6.4 ± 0.8	7.1 ± 0.8	5.2 ± 1	7.3 ± 0.9
Postprandial plasma glucose (mM)	11.5 ± 0.7	7.9 ± 0.9	11.7 ± 1.2	10.8 ± 0.9	11.9 ± 0.9
Glycosylated hemoglobin (%)	8.2 ± 0.3	8.3 ± 0.3	8.0 ± 0.4	7.6 ± 0.3	7.6 ± 0.3
Insulin dosage (IU/day)		50.3 ± 6		48.3 ± 6	
Serum triglycerides (mM)		1.2 ± 0.4		1.2 ± 0.3	
Total cholesterol (mM)		5.1 ± 0.3		5.0 ± 0.3	
HDL cholesterol (mM)		1.2 ± 0.07		1.2 ± 0.08	
Uric acid (μM)		219.4 ± 23.7		229.4 ± 35.7	

V_1, V_2, V_3: outpatient visits 1, 2, and 3.
H_1, H_2: hospitalization periods 1 and 2.

TABLE 4
Long-term trial: metabolic and renal consequences of 1 yr of enalapril administration

	0 mo	12 mo
Fasting plasma glucose (mM)	6.1 ± 0.7	5.6 ± 0.9
Postprandial plasma glucose (mM)	7.7 ± 0.8	10.3 ± 1.2
Glycosylated hemoglobin (%)	8.2 ± 0.3	8.0 ± 0.4
Insulin dosage (IU/day)	46.5 ± 6.7	46.2 ± 7.5
Serum triglycerides (mM)	1.2 ± 0.4	1.3 ± 0.3
Total cholesterol (mM)	5.2 ± 0.3	5.0 ± 0.3
HDL cholesterol (mM)	1.24 ± 0.07	1.31 ± 0.09
Uric acid (μM)	230 ± 21.7	252 ± 24
Kalemia (mM)	4.25 ± 0.1	4.3 ± 0.2
Natriuresis (mM)	112 ± 22	130 ± 17
Creatinine clearance (ml/min)	72 ± 10	83 ± 7
Albumin excretion rate (mg/24 h)	50.5 ± 37	12.2 ± 4.4
Urinary β_2-microglobulin (μg/24 h)	195 ± 66	228 ± 53
Urinary kallikrein activity (μg LBK/min)	14 ± 3	66 ± 21

LBK, lysylbradykinin.

decline with time. No clinical side effects due to the drug were observed.

Effects on the metabolism and kidney function. As shown in Table 4, 1 yr of treatment with enalapril did not modify the metabolism or the renal condition.

DISCUSSION

In this trial, it was decided to administer one daily dose of enalapril on the basis of the data reported by Bergstrand et al. (11), who showed that the efficacy and tolerance of once-daily and twice-daily regimens were similar. Our results are in keeping with previous findings for patients with mild to moderate hypertension. In monotherapy, enalapril was previously found to induce a significant drop in SBP and DBP in both the supine and upright positions (12,13). These results were confirmed here for the first time in a particular population consisting of insulin-dependent diabetic patients prone to suffer side effects due to antihypertensive drugs. Here, however, the significant reduction in blood pressure induced by enalapril was not accompanied by functional side effects or by any harmful consequences in metabolism or kidney function. The significant decrease in blood pressure was not associated with the reflex tachycardia previously observed with other drugs having a vasodilator component to their action, such as hydralazine, whose use is necessarily restricted in diabetic subjects because of the high prevalence of coronary heart disease in this population. The changes in blood pressure that occurred on standing were not influenced by enalapril and no postural hypotension was observed. In this small group, no functional side effects were reported by the patients during the long-term trial.

In hypertensive patients, diuretics (14) and β-blockers (15) may interfere with carbohydrate metabolism, and in insulin-treated diabetic patients, β-blockers may precipitate severe hypoglycemic episodes (16). Consequently, it is important to note that 1 yr of enalapril administration did not significantly alter daily insulin requirements or glycemic control, which was tightly monitored by self-determined capillary glucose and measurements of HbA_1. The deleterious effects of diuretics and β-blockers on blood lipid patterns have been repeatedly reported and were recently reviewed (17). No data are available about the influence of these drugs on hypertensive diabetic subjects; nevertheless, it is logical to assume that such adverse effects would be enhanced in the diabetic population. It is therefore of considerable interest that no changes were observed during enalapril treatment in the levels of triglycerides, total cholesterol, and HDL cholesterol. Because diuretics may induce severe hyperkalemia in diabetic patients, this effect was to be expected when such patients were treated with a converting enzyme inhibitor; however, in this study, as in earlier trials involving nondiabetic subjects, potassium levels did not change. The same results were observed by Sullivan et al. (18), who administered small doses of captopril for 3 mo to non-insulin-dependent diabetic hypertensive subjects. Monitoring of renal function is crucial when treating diabetic hypertensives. Enalapril did not modify glomerular filtration (assessed by creatinine clearance), nor did it significantly alter markers of diabetic nephropathy.

Urinary kallikrein activity, which is reduced in diabetic patients (19), was not modified, and neither was β_2-microglobulinuria, an index of tubular function. A nonsignificant reduction in microalbuminuria was observed. The lack of statistical significance was probably due to the small number of patients; only three of them had increased urinary albumin excretion before treatment. Note that for these three patients, microalbuminuria, a marker of incipient nephropathy (20), was markedly reduced during enalapril administration.

In conclusion, administration of 20 or 40 mg enalapril once daily to insulin-dependent subjects with mild to moderate hypertension was effective, well tolerated, and did not modify metabolic condition or renal function. Because such effects are difficult to obtain with the usual antihypertensive agents, the results of this study suggest that enalapril should be used once daily as a first step in the treatment of diabetic subjects with mild to moderate uncomplicated hypertension.

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