Effects of different antihypertensive drugs on plasma fibrinogen in hypertensive patients

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- 1 In order to evaluate whether treatment with different antihypertensive drugs would affect plasma fibrinogen levels, 118 mild to moderate essential hypertensive subjects, all males, aged 18 to 65 years, were randomly treated with amlodipine 10 mg, atenolol 100 mg, hydrochlorothiazide 25 mg or lisinopril 20 mg, all given once daily for 8 weeks.
- 2 Before and after 8 weeks' treatment, blood pressure (BP), heart rate (HR), fibrinogen, total cholesterol (TC), HDL-C, LDL-C, triglycerides (TG), plasma glucose, plasma uric acid, serum creatinine and serum potassium were evaluated.
- 3 All four medications significantly reduced BP values, although the BP lowering effect of lisinopril, amlodipine and atenolol was significantly greater compared with that of hydrochlorothiazide.
- 4 Plasma fibrinogen levels were unaffected by atenolol, hydrochlorothiazide and amlodipine, whereas they were significantly decreased by lisinopril (–11.2%, $P = 0.002$). This fibrinogen lowering effect was more evident in smokers (–17.7%) than in non smokers (–7.4%).
- 5 Atenolol and amlodipine did not significantly affect plasma lipids, hydrochlorothiazide increased TC, LDL-C and TG and reduced HDL-C; lisinopril increased HDL-C and decreased TC and LDL-C.
- 6 Hydrochlorothiazide increased plasma glucose and uric acid concentrations, which were unaffected by the other drugs. The diuretic also reduced serum potassium.
- 7 The results of this study indicate that lisinopril reduces levels of plasma fibrinogen and confirm that different antihypertensive drugs may elicit different metabolic effects, which may variously influence the overall risk profile of the hypertensive patients.

Keywords hypertension fibrinogen amlodipine atenolol hydrochlorothiazide lisinopril

Introduction

In recent years a series of epidemiological studies has shown that high fibrinogen levels represent a risk factor for cardiovascular morbidity and mortality [1–11]. Multiple mechanisms may contribute to this effect. These include increased blood viscosity [12], enhanced platelet adhesiveness and aggregation [13, 14] favouring the deposition of thrombus [15], decreased perfusion and tissue oxygenation [16]. Additionally, fibrinogen and its derivatives seem to be involved in both the initiation and sustained growth of atherosclerotic lesions [17–19].

Plasma fibrinogen values are reported to be elevated in arterial hypertension, where they are often associated with the presence of other established cardiovascular risk factors (smoking habit, diabetes, obesity, dyslipidaemia etc.) [1, 6, 20–23]. The combination of these risk factors greatly enhances the risk of hypertensives of developing coronary heart disease (CHD) and failure to influence satisfactorily these risk factors may be one of the possible explanations for the disappointing results of antihypertensive treatment on the incidence of CHD [24–27]. Conse-

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quently, to avoid CHD, optimal preventive management of hypertension requires comprehensive risk reduction beyond blood pressure control. A corollary to this approach is that antihypertensive drugs should not aggravate metabolic factors that may increase the risk of CHD and thus offset the benefits of antihypertensive therapy [26, 27].

Currently, little is known about the effects of the various antihypertensive medications on plasma fibrinogen [28–33]. The β -adrenoceptor blockers, propranolol and celiprolol, have been shown to lower plasma fibrinogen concentrations in patients with angina pectoris [30–31]. A fibrinogen lowering effect has been described also with prazosin [29] and the calcium antagonist nisoldipine [28], but interpretation of the data is difficult. In particular, it is not clear whether fibrinogen levels were decreased by the drugs *per se* or they decreased because some underlying disease process was corrected.

The aim of this study was to assess whether treatment of hypertension with four different classes of antihypertensive drugs would affect plasma fibrinogen levels and other metabolic parameters.

Methods

We studied 118 subjects with mild to moderate essential hypertension (DBP ≥ 95 and ≤ 115 mm Hg); they were male, aged 18 to 65 years and all belonged to the same working community, in which there was an established work-site hypertension detection and treatment program.

Patients with significant cardiovascular, pulmonary or systemic disease, hepatic or renal dysfunction, diabetes mellitus, obesity (body mass index > 30), plasma TG greater than 4.5 mmol l^{-1} were excluded from the study as were patients using lipid lowering drugs, ticlopidine, aspirin or other anti-inflammatory agents. All patients gave informed consent.

After a 4-week wash-out period on placebo, patients were assigned to receive amlodipine 10 mg ($n = 29$ patients), atenolol 100 mg ($n = 31$), hydrochlorothiazide 25 mg ($n = 28$) or lisinopril 20 mg ($n = 30$), for 8 weeks according to a randomized parallel-group, open design. The trial medications were all provided at the dosage of 1 tablet once daily. Patients were asked not to modify their dietary habit and life-style during the study.

Patients were evaluated after the initial wash-out period and at the end of the active treatment. At each visit, blood pressure (BP), heart rate (HR), body weight and height were measured. Blood samples were drawn from an antecubital vein with minimal stasis after a 12 h overnight fast and after at least 10 min of rest in the recumbent position for evaluation of fibrinogen, total cholesterol (TC), HDL-C, LDL-C, triglycerides (TG), blood glucose, uric acid, serum creatinine and serum potassium. Information was collected with regard to medical history and personal habits, especially smoking. BP was measured by the same observer using a standard mercury sphygmo-

manometer (Korotkoff I and V) after the subjects had been seated for 5 min. The average of three consecutive measurements, with at least 1 min interval between them, was recorded. HR was measured by pulse palpation for 30 s. Body weight and height were measured with the subjects barefoot and outer garments removed. Fibrinogen levels were measured in citrated plasma samples using a standard coagulation method [34]. Fibrinogen measurements were performed in duplicate and averaged. TC and TG were determined enzymatically (Chemetron Company); HDL-C was determined by the enzymatic method of Roschlau [35] after LDL and VLDL precipitation with polyethylene glycol 6000 by the method of Viikari [36]; LDL-C was calculated using the formula of Friedewald [37].

Data are presented as means $\pm$ s.e. mean. The statistical analysis was performed by analysis of variance to compare the treatment effects: the baseline values of parameters were used as the covariate, the difference between the baseline and the final value being used. Within treatments Student's *t*-test was used. For all calculations GLM, MEANS and UNIVARIATE SAS 6.04 procedures were used.

Results

The four randomized treatment groups were comparable with regard to the main demographic and clinical characteristics (Table 1).

As shown in Table 2, the four treatments produced a significant reduction in both SBP and DBP values as compared with baseline, although the BP lowering effect of amlodipine, atenolol and lisinopril was significantly greater as compared with that of hydrochlorothiazide.

HR mean values were affected neither by hydrochlorothiazide nor by amlodipine, whereas they were reduced by lisinopril and particularly by atenolol (Table 2).

Plasma fibrinogen levels were not affected by amlodipine, atenolol and hydrochlorothiazide, whereas they were significantly decreased by lisinopril (-11.2% , $P = 0.0002$) (Table 3). The effect of lisinopril on fibrinogen was statistically different from that of the other drugs. Table 3 shows the effects of antihypertensive treatment on plasma fibrinogen according to smoking habit: in all treatment groups, baseline fibrinogen levels were significantly higher in smokers than in non-smokers; treatment with amlodipine, atenolol and hydrochlorothiazide did not significantly affect fibrinogen values either in smokers or in non-smokers; unlike the other drugs, lisinopril significantly reduced plasma fibrinogen levels in both groups, although its fibrinogen lowering effect was more evident in smokers (-17.7% , $P < 0.001$) than in non-smokers (-7.4% , $P < 0.05$) (Figure 1).

Treatment with amlodipine and atenolol did not significantly influence plasma lipid values (Table 4). Hydrochlorothiazide produced a significant increase

Table 1 Main baseline characteristics of the patients of the four treatment groups

	<i>Atenolol</i>	<i>Hydrochlorothiazide</i>	<i>Amlodipine</i>	<i>Lisinopril</i>
Age (years)	48.33 ± 5.34	50.08 ± 6.04	52.34 ± 7.38	49.50 ± 5.82
Weight (kg)	75.74 ± 10.98	79.75 ± 12.95	76.97 ± 9.81	81.37 ± 12.28
Height (cm)	169.45 ± 6.74	170.46 ± 5.32	167.83 ± 8.17	170.03 ± 5.71
Smokers (<i>n</i>)	13	13	17	16
Non smokers (<i>n</i>)	18	15	12	14

Table 2 Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) values (means ± s.e. mean) before and after treatment with atenolol, hydrochlorothiazide, amlodipine and lisinopril and mean change induced by each drug

	<i>SBP (mm Hg)</i>			<i>DBP (mm Hg)</i>			<i>HR (beats min⁻¹)</i>		
	<i>Basal</i>	<i>Final</i>	<i>Mean change</i>	<i>Basal</i>	<i>Final</i>	<i>Mean change</i>	<i>Basal</i>	<i>Final</i>	<i>Mean change</i>
Atenolol	156.8 ± 1.3	138.6 ± 1.8	-18.2*‡	100.3 ± 0.7	85.7 ± 0.6	-14.6*‡	79.2 ± 0.9	64.1 ± 1.0	-15.1**
Hydrochlorothiazide	159.3 ± 1.2	147.2 ± 1.5	-12.1*	98.4 ± 0.4	86.9 ± 0.5	-11.5*	76.0 ± 1.0	75.6 ± 0.9	-0.4
Amlodipine	162.8 ± 1.5	147.5 ± 1.5	-15.3*‡	101.0 ± 0.8	86.2 ± 0.6	-14.8*‡	75.6 ± 0.9	79.3 ± 0.9	+3.7
Lisinopril	159.7 ± 0.9	141.5 ± 1.2	-18.2*‡	100.1 ± 0.5	86.0 ± 0.6	-14.1*‡	75.4 ± 0.6	72.4 ± 0.6	-3.0†

* = $P < 0.0001$ vs basal.** = $P < 0.0001$ vs basal and vs the other drugs.† = $P < 0.001$ vs basal.‡ = $P < 0.05$ vs hydrochlorothiazide.**Table 3** Values of plasma fibrinogen (mg dl⁻¹) (mean ± s.e. mean) before and after treatment with atenolol, hydrochlorothiazide, amlodipine and lisinopril and mean change induced from each drug. Data regarding all the patients, smokers and non-smokers are reported

	<i>All patients</i>			<i>Smokers</i>			<i>Non smokers</i>		
	<i>Basal</i>	<i>Final</i>	<i>Mean change</i>	<i>Basal</i>	<i>Final</i>	<i>Mean change</i>	<i>Basal</i>	<i>Final</i>	<i>Mean change</i>
Atenolol	317.2 ± 12.3	331.1 ± 12.9	+13.9	356.0 ± 16.6	372.5 ± 10.0	+16.5	289.2 ± 14.6	301.3 ± 18.1	+12.1
Hydrochlorothiazide	318.8 ± 13.7	325.5 ± 11.6	+6.7	376.7 ± 13.9	362.7 ± 15.1	-14	268.6 ± 12.3	293.3 ± 12.5	+24.7
Amlodipine	321.3 ± 12.3	311.6 ± 11.9	-9.7	344.9 ± 14.1	338.3 ± 14.2	-6.6	288.0 ± 18.7	273.7 ± 15.2	-14.3
Lisinopril	322.3 ± 14.5	279.6 ± 11.1	-42.6 ^{ab}	385.7 ± 15.1	317.0 ± 17.1	-68.7 ^c	266.8 ± 10.5	246.9 ± 8.7	-19.9 ^d

^a = $P < 0.01$ vs basal and vs amlodipine.^b = $P < 0.001$ vs atenolol and hydrochlorothiazide.^c = $P < 0.001$ vs basal and vs the other drugs.^d = $P < 0.05$ vs basal and vs atenolol and hydrochlorothiazide.

in TC (+7.5%, $P = 0.0003$), LDL-C (+12.3%, $P = 0.0013$) and TG (+13.8%, $P = 0.0007$) and a decrease in HDL-C (-8.05%, $P = 0.06$), Lisinopril increased HDL-C (+9.47%, $P = 0.001$) and decreased TC (-2.2%, $P < 0.05$) and LDL-C (-3.9%, $P = 0.04$), with no significant effect on TG, although a trend toward a decrease in this parameter was observed.

Hydrochlorothiazide significantly increased plasma glucose (+3.28%, $P = 0.0013$), uric acid (+6.96%, $P = 0.0018$) and serum creatinine (+5.10%, $P = 0.004$), which were unaffected by the other treatments (Table 5). Serum potassium was significantly lowered

by hydrochlorothiazide (-5.47%, $P = 0.0025$) and increased by lisinopril (+5.46%, $P = 0.005$).

None of the drugs produced significant changes in body weight. No changes in lifestyle was recorded in any patient.

Discussion

The results of this study confirm that, beyond their lowering effects on BP values, different antihyperten-

Figure 1 Percent changes in plasma fibrinogen mean values after treatment with atenolol, hydrochlorothiazide, amlodipine and lisinopril. □ all patients, ▨ non-smokers, ■ smokers. * = $P < 0.05$ vs basal and vs atenolol and hydrochlorothiazide. ** = $P < 0.01$ vs basal and vs amlodipine. *** = $P < 0.001$ vs basal and vs the other drugs. ° = $P < 0.001$ vs atenolol and hydrochlorothiazide.

sive drugs may exert different metabolic effects, thus variously influencing the overall risk profile of the hypertensive patients.

As reported in the literature [38, 39], hydrochlorothiazide treatment worsened the serum lipid profile and other metabolic variables, such as plasma glucose, uric acid and serum potassium. Atenolol did not significantly affect any of the metabolic parameters studied, thus indicating that β -selective β -adrenoceptor blockers have less impact on plasma glucose and lipids than non-selective ones, in agree-

ment with earlier reports [40, 41]. Our data also confirm the neutral effects of amlodipine on lipid and glucose levels [42]. Lisinopril influenced neither plasma glucose nor uric acid and beneficially affected the serum lipid profile, by increasing HDL-C and decreasing TC and LDL-C, observations in agreement with others reported in the literature [43–45].

The most interesting finding of this study, however, was the fibrinogen lowering effect of lisinopril. Such an effect, which was more evident in hypertensive smokers as compared with non-smokers, was not observed with any of the other antihypertensive medications and seemed not to depend on BP reduction. There are several difficulties in interpreting this finding, which, to our knowledge, has not been reported by other authors and obviously needs to be confirmed. In particular, it remains to be established whether the fibrinogen lowering effect of lisinopril is due to the effect of the drug on associated variables, e.g. plasma lipids, or to a direct effect of the drug, perhaps through inhibition of some steps of the regulatory mechanisms which control the hepatic synthesis of fibrinogen. In this regard, a role of the kallikrein-kinin system cannot be excluded. On the other hand, data available on other drugs affecting plasma fibrinogen values (ticlopidine, fibrates, N3-fatty acids, pentoxifylline etc.) are only circumstantial and inconclusive with respect to the mechanisms involved [46, 47]. We cannot explain the more pronounced fibrinogen lowering effect of lisinopril in smokers, i.e. in subjects with higher baseline fibrinogen values, as compared with non smokers. Regression to the mean may partly explain this phenomenon.

Further long-term studies are needed to evaluate better the effects of ACE-inhibitors as well as other antihypertensive medications on plasma fibrinogen.

Table 4 Values of total cholesterol (TC), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C) and triglycerides (TG) before and after treatment with atenolol, hydrochlorothiazide, amlodipine and lisinopril and mean change induced by each drug

	TC (mmol l ⁻¹)			HDL-C (mmol l ⁻¹)			LDL-C (mmol l ⁻¹)			TG (mmol l ⁻¹)		
	Basal	Final	Mean change	Basal	Final	Mean change	Basal	Final	Mean change	Basal	Final	Mean change
Atenolol	5.95 ± 0.19	5.86 ± 0.17	-0.09	1.02 ± 0.05	0.99 ± 0.04	-0.33	4.20 ± 0.18	4.08 ± 0.16	-0.12	1.59 ± 0.09	1.71 ± 0.09	+0.12
Hydrochlorothiazide	6.01 ± 0.21	6.45 ± 0.23	+0.44 ^{dih}	1.15 ± 0.06	1.02 ± 0.05	-0.13 ^{bh}	4.11 ± 0.18	4.57 ± 0.21	+0.46 ^{dih}	1.65 ± 0.14	1.87 ± 0.16	+0.22 ^{cef}
Amlodipine	6.08 ± 0.21	6.09 ± 0.24	+0.01	1.19 ± 0.06	1.18 ± 0.05	-0.01	4.13 ± 0.22	4.17 ± 0.24	+0.04	1.65 ± 0.09	1.62 ± 0.11	-0.03
Lisinopril	6.03 ± 0.17	5.87 ± 0.14	-0.16 ^b	1.10 ± 0.05	1.18 ± 0.04	+0.08 ^{cg}	4.19 ± 0.17	3.98 ± 0.13	-0.21	1.62 ± 0.09	1.55 ± 0.07	-0.07 ^g

^a = $P < 0.001$ vs basal.

^b = $P < 0.05$ vs basal.

^c = $P < 0.005$ vs basal.

^d = $P < 0.01$ vs basal.

^e = $P < 0.05$ vs amlodipine.

^f = $P < 0.005$ vs lisinopril.

^g = $P < 0.05$ vs atenolol.

^h = $P < 0.005$ vs amlodipine.

ⁱ = $P < 0.001$ vs lisinopril and atenolol.

Table 5 Values of serum creatinine, uric acid, blood glucose and serum potassium (means $\pm$ s.e. mean) before and after treatment with atenolol, hydrochlorothiazide, amlodipine and lisinopril and mean change induced by each drug

	Serum creatinine (mmol l ⁻¹)			Uric acid (mmol l ⁻¹)			Blood glucose (mmol l ⁻¹)			Serum potassium (mmol l ⁻¹)		
	Basal	Final	Mean change	Basal	Final	Mean change	Basal	Final	Mean change	Basal	Final	Mean change
Atenolol	86.7 $\pm$ 1.9	86.1 $\pm$ 1.5	-0.6	304.6 $\pm$ 13.9	304.9 $\pm$ 12.2	+0.3	5.05 $\pm$ 0.11	5.11 $\pm$ 0.10	+0.06	4.45 $\pm$ 0.15	4.43 $\pm$ 0.06	-0.02
Hydrochlorothiazide	84.8 $\pm$ 1.8	88.6 $\pm$ 1.5	+3.8 ^{cd}	320.2 $\pm$ 16.2	342.2 $\pm$ 19.8	+22.0 ^{ce}	4.98 $\pm$ 0.13	5.23 $\pm$ 0.14	+0.25 ^{cf}	4.41 $\pm$ 0.10	4.13 $\pm$ 0.06	-0.28 ^{be}
Amlodipine	90.3 $\pm$ 3.8	84.6 $\pm$ 1.4	-5.7	312.6 $\pm$ 12.0	311.1 $\pm$ 11.6	-1.5	4.96 $\pm$ 0.05	5.07 $\pm$ 0.08	+0.1	4.39 $\pm$ 0.09	4.40 $\pm$ 0.06	+0.01
Lisinopril	87.4 $\pm$ 2.8	89.4 $\pm$ 1.3	+2.0 ^{ad}	316.1 $\pm$ 12.7	311.5 $\pm$ 11.1	-4.6	4.98 $\pm$ 0.13	4.86 $\pm$ 0.09	-0.1	4.37 $\pm$ 0.08	4.58 $\pm$ 0.06	+0.21 ^{bgh}

^a = $P < 0.05$ vs basal.^b = $P < 0.001$ vs basal.^c = $P < 0.005$ vs basal.^d = $P < 0.05$ vs amlodipine.^e = $P < 0.005$ vs the other drugs.^f = $P < 0.005$ vs lisinopril.^g = $P < 0.005$ vs amlodipine.^h = $P < 0.01$ vs atenolol.

From our data, however, lisinopril would seem to present some advantage over the other antihypertensive drugs in terms of non exacerbation or improvement of coronary risk profile. Besides lowering

blood pressure, it seems to reduce fibrinogen levels and improve the lipid pattern, which might be of great value in the prevention of CHD in hypertensive patients.

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