Urapidil Treatment Decreases Plasma Fibrinogen Concentration in Essential Hypertension

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The effects of antihypertensive drugs on cardiovascular metabolic risk factors were monitored in 42 patients with essential hypertension (diastolic blood pressure [DBP] >95 mm Hg). In a double-blind randomized parallel-group study, they were treated with atenolol 50 mg once per day (n = 25) or urapidil 60 mg twice per day (n = 17), a peripheral α_1-receptor blocker with an additional central serotonin 1A (5HT1A) receptor agonistic effect, for 12 weeks. Plasma fibrinogen concentration decreased by 24% ($P < .0001$) during urapidil treatment and by 9% ($P = .05$) during atenolol treatment, with the effects of the two drugs differing significantly. Plasminogen activator inhibitor (PAI) activity tended to increase by 17% (nonsignificant [NS]) in the atenolol-treated group and to decrease by 4% (NS) in the urapidil group. Differences between the effects of the two drugs on very-low-density lipoprotein (VLDL) triglycerides (TG) and on total TG were significant. During urapidil medication, these two parameters were reduced by 22% and 13%, respectively, but the changes were nonsignificant ($P = .11$ and $P = .14$, respectively). In contrast, atenolol treatment caused a significant increase in both VLDL TG and total TG of 31% and 21%, respectively. Hemoglobin A_{1c} (HbA_{1c}) increased by 4% ($P = .06$) during atenolol treatment, but was unaffected by urapidil. There were no significant changes within or between atenolol- and urapidil-treated groups regarding glucose disposal on an oral glucose tolerance test (OGTT) or the insulin sensitivity index on a hyperinsulinemic-euglycemic clamp test. In conclusion, urapidil treatment was characterized by neutral or favorable effects on several variables associated with the metabolic syndrome. Atenolol treatment had neutral properties in some metabolic aspects, but deleterious effects on lipid status.

THE VALUE OF antihypertensive treatment in young, middle-aged, and elderly patients is well established.[1-4] Several prospective studies have indicated that antihypertensive treatment reduces the risk for stroke, but in a number of studies it has been found less effective in diminishing the risk for coronary heart disease in middle-aged people.[4] Different possible explanations for this discrepancy have been discussed, one of which is that the drugs used in these trials may have effects on other cardiovascular risk factors. Insulin-dependent glucose uptake is lower and impaired glucose tolerance more common in hypertensive versus normotensive men and women.[5] An atherothrombogenic metabolic syndrome including insulin resistance, glucose intolerance, hyperlipidemia, hyperfibrinogenemia, and impaired fibrinolysis has been considered.[6] Several of the most frequently prescribed antihypertensive drugs, especially β-adrenergic blockers and thiazide diuretics, have adverse effects on lipoprotein status and glucose metabolism, thus deteriorating insulin-stimulated glucose uptake further.[7,8] Prazosin and doxazosin, α_1-blockers, have been shown to improve insulin sensitivity and to decrease serum triglycerides (TG) and cholesterol.[9-11] These properties may provide some theoretical advantages for these drugs over β-blockers and diuretics, from the cardiovascular point of view.

Urapidil is a new antihypertensive drug that blocks peripheral α_1-adrenergic receptors but also stimulates central serotonin 1A (5HT1A) receptors, decreasing the sympathetic tone and increasing the vagal tone, which may imply less tachycardia with vasodilatation or decreasing blood pressure.[12-18]

SUBJECTS AND METHODS

The study was undertaken to monitor the effects of urapidil and atenolol on cardiovascular risk factors associated with insulin sensitivity, glucose and lipoprotein metabolism, plasma fibrinogen concentration, and plasma plasminogen activator inhibitor (PAI) activity in patients with essential hypertension. The protocol was approved by the Human Ethics Committee of the Medical Faculty of Uppsala University. Informed consent was obtained from all patients after the protocol, nature, and purpose of the study and possible side effects had been fully explained.

Seventy-eight patients with newly detected essential hypertension or already undergoing antihypertensive treatment initially entered the study. All patients provided a detailed medical history and underwent a physical examination that also included an electrocardiogram and a routine laboratory investigation. Patients with acute or chronic infectious diseases, liver diseases, renal insufficiency, psychic disorders, or diseases of the central nervous system were excluded, as well as patients with unstable angina pectoris or auscultatory findings indicating stenosis of the aortic valve or carotid artery. Previous treatment with diuretics within the previous 6 months was also a reason for exclusion.

The study was designed as a double-blind randomized parallel-group investigation. After withdrawal of all antihypertensive drugs, 78 patients were randomized to receive placebo + atenolol or placebo + urapidil. Five patients did not complete the single-blind placebo run-in period of at least 4 to 6 weeks, and 23 patients did not meet the inclusion criterium for supine diastolic blood pressure (DBPsup), 95 to 115 mm Hg, on two separate occasions during the placebo period. The remaining 50 patients (clinical characteristics and family history of hypertension and/or diabetes mellitus shown in Table 1) were characterized metabolically at the end of the placebo period, and received active treatment with urapidil 60 mg twice daily or atenolol 50 mg once daily for 12 weeks.

Blood pressure was measured every fourth week. At the end of the placebo period and the end of the period of active treatment, ambulatory blood pressure monitoring (ABPM) for 24 hours, a

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Table 1. Clinical Characteristics of the Hypertensive Patients (all white) Before Active Drug Treatment

Characteristic	Urapidil	Atenolol
No. of patients	23	27
Men/women (women >50 yr)	11/12 (9)	15/12 (7)
Withdrew/side effects (men/women)	2/3	1/1
Additional drug treatment (men/women)	1/0	0/0
Completed study (men/women)	17 (8/9)	25 (14/11)
Age (yr)	60 ± 9	55 ± 9
Waist to hip ratio	0.93 ± 0.06	0.94 ± 0.07
BMI (kg/m^2)	27.6 ± 5.7	27.5 ± 3.6
No. of smokers	3	9
Heredity		
Hypertension (single/double)	9/2	12/4
Diabetes mellitus (single/double)	5/0	4/1
Hypertension and diabetes (single/double)	4/0	4/0

NOTE. The mean values (±SD) for age, waist to hip ratio, and BMI, as well as the family history of hypertension and/or diabetes, ie, history of the diseases in 1 parent (single) or both parents (double), are given.

hyperinsulinemic-euglycemic clamp test, and an OGTT were performed, lipoprotein status was assessed, serum concentrations of electrolytes, urate, and free fatty acids (FFA) and plasma concentrations of fibrinogen, PAI activity, and urapidil were measured, and routine clinical laboratory tests were performed. The patients were seen by the same observers at the same time of day 2 to 4 hours after capsule intake.

Blood pressure measurements were made in the right arm with a cuff of appropriate size. Systolic blood pressure (SBP) and DBP were defined as Korotkoff phases I and V, respectively. Blood pressure was measured to the nearest millimeter of mercury with a sphygmomanometer twice after a 10-minute rest and twice after 1 minute in the standing position. The mean of the two measurements in each position was recorded as the blood pressure. Pulse rate was determined by palpation of the radial artery over a 30-second period after 10 minutes in the supine position and after 1 minute in the standing position.

The 24-hour ABPM was performed in the left arm (Accutracker II; Suntech Medical Instruments, Raleigh, NC) starting at 11 AM, with recordings every 30 minutes during the daytime (6 AM to 11 PM) and every hour during the night (11 PM to 6 AM). Nighttime dip was calculated as the difference between nighttime and daytime mean SBP and DBP, respectively. Preset editing criteria omitted all recordings of zero, heart rate less than 30/min, SBP less than 70 or greater than 270 mm Hg, and DBP greater than 170 mm Hg, or a difference between SBP and DBP less than 10 mm Hg. The first value was excluded.

Insulin sensitivity was measured by the hyperinsulinemic-euglycemic clamp technique as described by De Fronzo et al.[19] The insulin (Actrapid Human; Novo, Copenhagen, Denmark) infusion rate was 56 $mU/m^2/min$ in all subjects. Plasma insulin was assayed with a radioimmunoassay kit (Phadeseph Insulin RIA; Pharmacia, Uppsala, Sweden). Plasma insulin concentrations attained during the insulin infusion in our study have been found at our laboratory to almost completely suppress hepatic glucose production, both in hypertensive and in diabetic subjects, even in the presence of insulin resistance.[20] The target level for plasma glucose during the clamp test was 5.1 mmol/L, which was maintained by measuring plasma glucose concentration every 5 minutes (Beckman Glucose Analyzer II; Beckman Instruments, Fullerton, CA) and adjusting the rate of glucose infusion (Glukos 20%; Pharmacia) with the MiniMed III (MiniMed Technologies, Sylmar, CA).

Glucose uptake (M) was calculated on the basis of the amount of glucose infused, and is expressed as milligrams per kilogram body weight per minute. The insulin sensitivity index (M/I ratio) was calculated by dividing the mean glucose uptake (M) by the mean insulin concentration (I) during the steady-state phase, ie, in the last 60 minutes, of the clamp study (M value/mU/L × 100). The M/I ratio is a more exact measure of tissue sensitivity to insulin than mean glucose uptake alone, since drug treatment and altered insulin metabolism may influence plasma insulin concentration despite an unchanged insulin infusion rate.

For the OGTT, plasma glucose and insulin concentrations were measured before and 30, 60, 90, 120, and 180 minutes after ingestion of 75 g glucose in 150 mL water. The area under the curve (AUC) analyses were performed according to the trapezoidal rule estimate.

TG and cholesterol concentrations in serum were measured by enzymatic techniques (Boehringer, Mannheim, Germany) in a Monarch 2000 (Instrumentation Laboratory, Lexington, MA) centrifugal analyzer. Very-low-density lipoprotein (VLDL) was separated by ultracentrifugation at a density of 1.006. A magnesium chloride/phosphotungstate technique was used to precipitate low-density lipoprotein (LDL). FFA in serum were determined by an enzymatic colorimetric method (Wako Chemical, Neuss, Germany).

PAI activity in plasma was determined by a two-stage enzymatic assay (Spectrolyse/pL; Biopool, Umea, Sweden). Plasma fibrinogen concentration was measured by an immunochemical nephelometric method using the Array Protein System (Beckman Instruments). Hemoglobin A_{1c} (HbA_{1c}) assays and routine laboratory tests were performed at the Department of Clinical Chemistry, University Hospital, Uppsala. Serum urapidil concentration was measured by high-performance liquid chromatography followed by UV detection[21] at Laboratories Byk France (Le Mee Sur Seine, France). Smoking habits and degree of physical activity during leisure time and at work were reported on a questionnaire. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Statistics

For variables with a skewed distribution (DBPsup, DBP standing, pulse rate standing, VLDL TG, VLDL cholesterol, HDL TG, HDL cholesterol, serum total TG, M/I ratio, fibrinogen, $AUC_{insulin}$, and $AUC_{glucose}$), logarithmic transformation was performed. A two-way ANOVA model was used to test changes within and between groups over time. All comparisons were made with the results at the end of the placebo period. Least-square means are the basis of tests and estimates in the analysis, and the reported significance levels correspond to these calculations. To elucidate the interdependence of different variables, stepwise multiple regression analyses were applied. P less than .05 was considered statistically significant. Statistical analyses were performed with the statistical program package, Statistical Analysis System, and JMP (SAS Institute Inc, Cary, NC).

RESULTS

Forty-two patients with essential hypertension completed the study, 17 treated with urapidil and 25 with atenolol (Table 1). Seven of 50 patients remaining after exclusions, five in the urapidil-treated group and two in the atenolol-treated group, were withdrawn from active treatment because of side effects or insufficient blood pressure reduction. One urapidil-treated patient used a prohibited drug, and his results were not included (Table 2).

The degree of physical activity during leisure time or at

Table 2. Patients Who Withdrew From the Study During Active Treatment With Urapidil and Atenolol

Patient No.	Sex	Drug	Reason	Period on Active Drug
19	M	U	BP 210/115-120	4 wk
33	F	U	Urinary incontinence	6 wk
35	M	U	Nasal congestion, headache	4 wk
41	F	A	Tiredness, nightmares, vertigo, bradycardia	2 d
45	M	A	Vertigo	3 wk
50	F	U	Tiredness, headache	5 wk
53	F	U	BP 158/120, headache	2 wk
10	M	U	Treatment with additional drug (niceritrol)	

Abbreviations: U, urapidil; A, atenolol.

work was reported to be decreased by two urapidil-treated patients and one atenolol-treated patient. Four patients in the atenolol-treated group reported increased physical activity. Two patients in the latter group changed their smoking habits—one started and the other stopped.

At the end of the initial placebo period, there were no significant differences ($P < .05$) in basic metabolic variables between the two treatment groups (Table 3). However, SBPsup was significantly higher in the group randomized for urapidil treatment (Table 4).

Plasma fibrinogen concentration was correlated with SBPsup ($r = .31$, $P < .05$), HbA_{1c} ($r = .38$, $P < .02$), and PAI activity ($r = .38$, $P < .02$), but only the correlation between plasma fibrinogen and PAI activity remained significant in multiple testing including SBPsup, HbA_{1c}, and PAI activity as regressors.

PAI activity was correlated with VLDL TG ($r = .61$, $P < .0001$), total TG ($r = .61$, $P < .0001$), mean fasting insulin ($r = .61$, $P < .0001$), BMI ($r = .59$, $P < .0001$), and fasting blood glucose ($r = .42$, $P < .007$), and inversely related to the M value and M/I ratio for the hyperinsulinemic-euglycemic clamp test ($r = -.45$, $P < .004$ and $r = -.41$, $P < .009$, respectively). In multiple testing, the correlations between PAI activity on one hand and VLDL TG, mean fasting insulin, and plasma fibrinogen on the other remained significant with a high explanatory value of 61% when the effect of BMI was considered. Correlations between PAI activity and the fasting blood glucose, M value, or M/I ratio remained significant when plasma fibrinogen was included but not when VLDL TG or mean fasting insulin were included in the analysis. The correlation between PAI activity and fasting blood glucose did not remain at a significant level when the M/I ratio was included.

Table 3. Adjusted Mean Values (±SD) for Plasma Fibrinogen Concentration and PAI Activity and Serum Total TG and Cholesterol Different Subfraction Concentrations at the End of the Placebo Period Before the Start of Active Treatment With Urapidil or Atenolol

Parameter	Urapidil	Atenolol
Plasma		
Fibrinogen (g/L)	3.4 ± 0.6	3.0 ± 0.6
PAI activity (U/mL)	19.5 ± 9.4	19.3 ± 9.4
Serum		
TG (mmol/L)	1.5 ± 0.7	1.5 ± 0.7
Cholesterol (mmol/L)	6.4 ± 1.1	5.5 ± 0.9
VLDL TG (mmol/L)	1.0 ± 0.7	1.0 ± 0.7
VLDL cholesterol (mmol/L)	0.4 ± 0.2	0.4 ± 0.4
LDL TG (mmol/L)	0.4 ± 0.1	0.4 ± 0.1
LDL cholesterol (mmol/L)	4.5 ± 1.1	3.9 ± 0.8
HDL TG (mmol/L)	0.1 ± 0.1	0.1 ± 0.1
HDL cholesterol (mmol/L)	1.4 ± 0.3	1.2 ± 0.3

NOTE. There were no significant ($P < .05$) differences in the variables between the 2 groups randomized for the different drugs.

Body weight remained constant in both the urapidil- and atenolol-treated patients.

Heart rate and SBP and DBP in both the supine and standing positions decreased significantly in both groups after active treatment. However, urapidil treatment decreased SBPsup significantly more than treatment with atenolol. However, when the data were adjusted for the difference in SBPsup at baseline between the two treatment groups, there was no difference in the capacity to decrease blood pressure between the two tested drugs. The reduction in heart rate in the standing position was significantly more pronounced during atenolol treatment (Table 4). The 24-hour ABPM showed a difference between the blood pressure–reducing profiles of the two drugs. Atenolol reduced or tended to reduce SBP and DBP throughout the day and night, whereas urapidil reduced SBP and DBP during the morning and daytime but not during the night (Fig 1). There was no difference between the two drug-treated groups regarding the extent of nighttime SBP or DBP decrease. In urapidil-treated subjects, there were no significant correlations between the plasma drug concentration and the changes in heart rate or blood pressure variables.

Fibrinogen decreased by 24% ($P < .0001$) during urapidil treatment and by 9% ($P = .05$) during atenolol treatment, which indicates a significant difference between the effects of the two drugs (Fig 2A). This difference remained significant when the participants who altered their smoking habits during the study were excluded from the statistical calculations. Patients with a high plasma urapidil concentration showed the most pronounced decrease in PAI activity (Fig 3). PAI activity decreased by 4% (nonsignificant [NS]) in the urapidil group and increased by 17% (NS) in the atenolol group. The difference between the effects of the two drugs was not significant in men and women combined. However, in the urapidil-treated group, there was a significant difference ($P < .04$) between the reduced PAI activity in the men (−27%, $P < .05$) and the change among the women (+18%, NS). In the atenolol-treated group, there was no significant difference between the changes in PAI activity in men and women, +24% (NS) and +9% (NS), respectively. The difference between changes in PAI activity in atenolol- and urapidil-treated men was significant ($P < .01$; Fig 2B). In the atenolol-treated group and in the

Table 4. Adjusted Mean Values (±SD) for SBP, DBP, and Pulse Rate in Supine and Standing Positions After Initial Placebo Period and the Changes After 3 Months on Urapidil or Atenolol Treatment

Variable	After Initial Placebo Period (time 0)	*P* for Difference Between Groups at time 0	Effect of Treatment			*P* for Difference Between Treatment Regimens
			Δ(3-0)	%	*P* for Δ(3-0)	
Supine						
SBP (mm Hg)						
Urapidil	173 ± 14	.0025	−21	−12	.0001	.07
Atenolol	152 ± 14		−9	−6	.02	
DBP (mm Hg)						
Urapidil	102 ± 5	NS	−13	−12	.0001	NS
Atenolol	101 ± 4		−12	−12	.0001	
Pulse (beats per min)						
Urapidil	76 ± 9	NS	−10	−13	.0001	NS
Atenolol	74 ± 10		−18	−24	.0001	
Standing						
SBP (mm Hg)						
Urapidil	166 ± 18	NS	−20	−12	.0001	NS
Atenolol	156 ± 15		−17	−11	.0001	
DBP (mm Hg)						
Urapidil	107 ± 7	NS	−15	−14	.0001	NS
Atenolol	107 ± 6		−11	−10	.0001	
Pulse (beats per min)						
Urapidil	84 ± 12	NS	−9	−10	.0001	.0003
Atenolol	82 ± 13		−21	−26	.0001	

Abbreviation: Δ(3-0), change after 3 months.

two treated groups combined, the change in PAI activity correlated with the change in fibrinogen concentration ($r = .56, P < .005$ and $r = .51, P < .001$, respectively).

During urapidil treatment, the VLDL TG fraction and total TG decreased by 22% and 13%, respectively, but the changes were not significant ($P = .11$ and $P = .14$, respectively). In contrast, atenolol treatment resulted in significantly higher VLDL TG, LDL TG, and total TG (31%, 8%, and 21%, respectively). Differences between the effects of the two drugs on VLDL TG and total TG were significant (Fig 4).

No statistically significant changes appeared within the two groups, and there were no significant differences in serum FFA between them.

During the steady-state period of the hyperinsulinemic-euglycemic clamp test, the glucose infusion rate (M) increased by 10% ($P = .09$) in urapidil-treated patients. The M value also showed a small increase (6%, NS) in the atenolol-treated group. The insulin sensitivity index, the ratio, M/I, tended to increase (4%, NS) in the urapidil-treated group (Table 5). When all patients who reported changes in the degree of physical activity during the period of active treatment were excluded from statistical calculations, there was a decrease in the M/I ratio (6%, NS) in the atenolol-treated group and an increase (2%, NS) in the group treated with urapidil, but the differences between the effects of the two tested drugs were not significant.

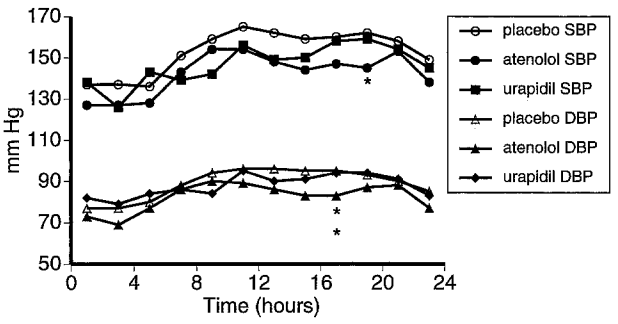

Fig 1. Twenty-four-hour ABPM during atenolol and urapidil treatment. Differences between the effects of the 2 drugs are indicated. For illustrative purposes, the mean values in the total study group at the end of the placebo period are shown. Values obtained at the end of each drug treatment period were calculated on the basis of the percentage change in comparison to the respective placebo value. *$P < .05$, **$P < .01$.

At the OGTT, the area under the glucose curve ($AUC_{glucose}$) and the area under the insulin curve ($AUC_{insulin}$) did not change significantly during either drug treatment, and the differences between the effects of the two drugs were not significant.

Fasting blood glucose and fasting plasma insulin were not affected by either urapidil or atenolol. However, HbA_{1c} increased by 4% ($P = .06$) of the baseline value during atenolol treatment (Table 5).

The uric acid concentration increased by 7% ($P < .02$) in atenolol-treated patients, but was unaffected by urapidil treatment. The hemoglobin concentration and hematocrit remained unaffected in both drug-treated groups.

With regard to sex-related differences in drug effects, the only one observed was for PAI activity.

DISCUSSION

The urapidil and atenolol doses used in this study seem equipotent with regard to the effect on blood pressure. The difference in SBPsup at baseline between the two groups is probably explained by the moment of randomization, which

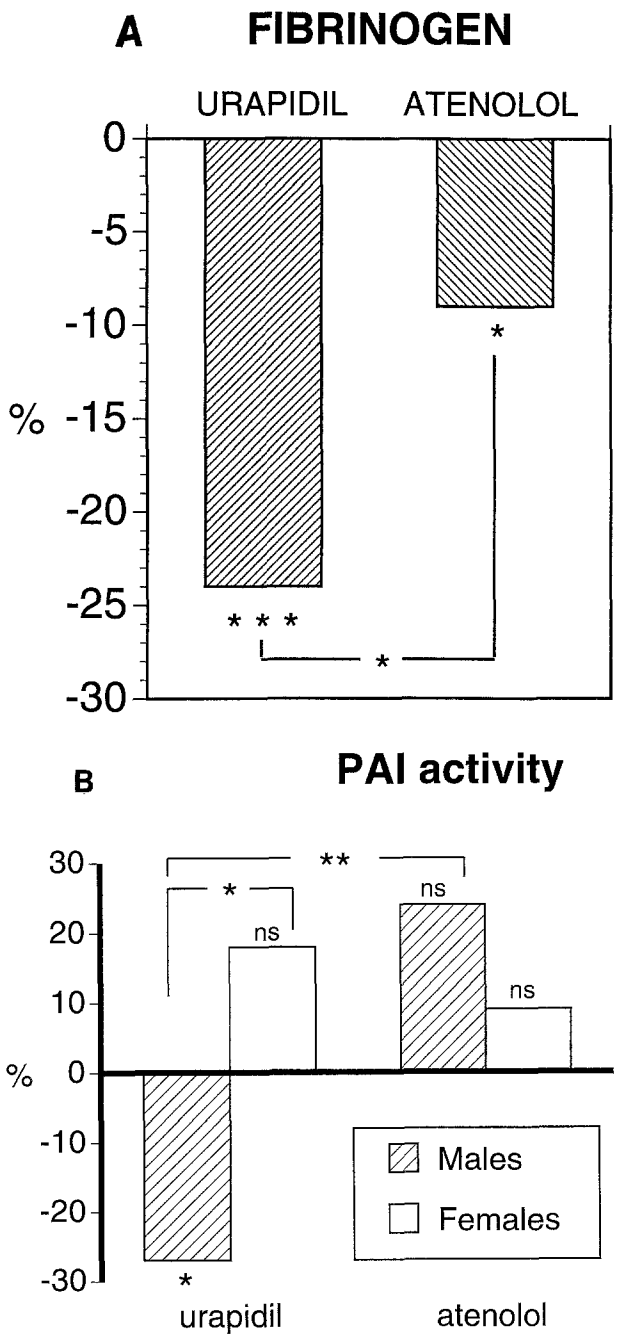

Fig 2. Changes (%) in plasma fibrinogen concentration (A) and plasma PAI activity (B) during atenolol and urapidil treatment. *P < .05, **P < .01, ***P < .001.

occurred contemporarily with the withdrawal of previous medication, ie, before the placebo period. There was no significant correlation between smoking habit and SBPsup at baseline.

The reduction in heart rate was less pronounced in urapidil-treated patients than in those treated with atenolol. In two previous studies of treatment with prazosin, an α-blocker with no central 5HT1A agonistic effect, heart rate increased by 3% in the supine position, but the blood pressure reduction was less pronounced than in the present study.[8,10] Urapidil has been reported to cause a significantly

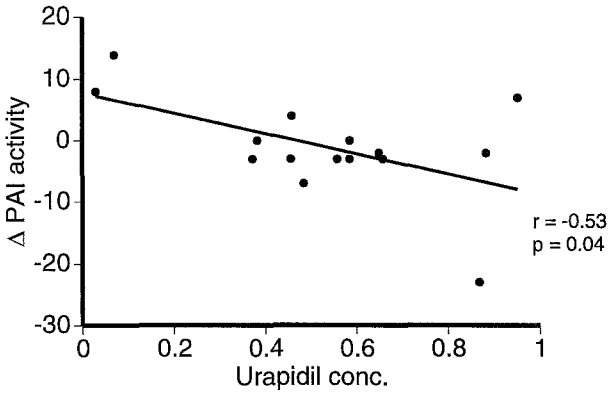

Fig 3. During urapidil treatment, the change (Δ) in PAI activity was inversely correlated with the plasma urapidil concentration.

smaller increase in heart rate than prazosin despite a blood pressure decrease of similar magnitude in patients with mild hypertension.[18] For a given level of noradrenaline, heart rate has been found to be slower with urapidil than with prazosin.[17] Thus, if urapidil treatment reduces heart rate to a greater extent than reported for other α_1-blockers, this may partly be explained by the 5HT1A agonistic properties of this α-blocker.

During ABPM, the two drugs tested in the present study showed somewhat different blood pressure–reducing profiles. However, statistically, there were few points in time at which there was a significant difference between the drugs' effects, and this was the case particularly in the morning hours when the metabolic investigations were performed.

Plasma fibrinogen decreased by 24% during urapidil treatment, whereas atenolol had a significantly weaker effect. Several prospective studies, including the Framing-

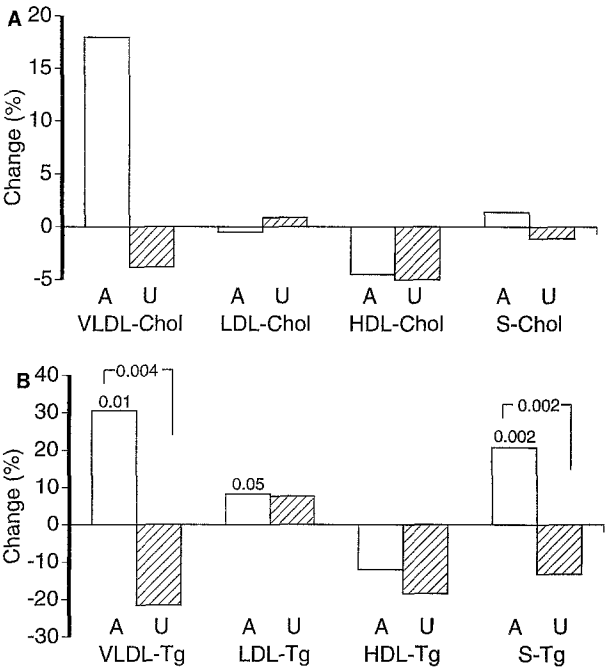

Fig 4. Changes (%) in serum cholesterol (A) and TG (B) during atenolol (A) and urapidil (U) treatment.

Table 5. Metabolic Characteristics of the Hypertensive Patients After the Initial Placebo Run-in Period (time 0)

Variable	After Initial Placebo Period (time 0)	*P* for Difference Between Groups at time 0	Effect of Treatment			*P* for Difference Between Treatment Regimens
			Δ(3-0)	%	*P* for Δ	
HbA_{1c} (%)						
Urapidil	4.6 ± 0.5	NS	0	1	NS	NS
Atenolol	4.3 ± 0.4		+0.2	4	.06	
fP insulin (mU/L)						
Urapidil	11.7 ± 4.8	NS	−0.2	−1	NS	NS
Atenolol	11.8 ± 5.6		−0.2	−2	NS	
fP glucose (mmol/L)						
Urapidil	5.8 ± 0.5	NS	0	1	NS	NS
Atenolol	5.9 ± 0.6		0	1	NS	
OGTT						
$AUC_{glucose}$						
Urapidil	72 ± 40	NS	−10	−13	NS	NS
Atenolol	57 ± 29		−7	−13	NS	
$AUC_{insulin}$						
Urapidil	1,095 ± 754	NS	+37	+3	NS	NS
Atenolol	1,014 ± 443		−73	−7	.08	
Clamp						
Insulin 120 min						
Urapidil	98 ± 22	NS	+5	+6	NS	NS
Atenolol	101 ± 19		+7	+7	.02	
M value 60-120 min						
Urapidil	4.5 ± 1.8	NS	+0.4	+10	.09	NS
Atenolol	4.5 ± 1.9		+0.2	+6	NS	
M/I ratio 60-120 min						
Urapidil	4.7 ± 2.3	NS	+0.2	+4	NS	NS
Atenolol	4.6 ± 2.5		0	0	NS	

NOTE. Adjusted mean values (±SD) for HbA_{1c}, fasting plasma insulin and glucose, $AUC_{glucose}$ and $AUC_{insulin}$ during the OGTT, insulin-mediated glucose disposal measured by the hyperinsulinemic-euglycemic clamp, plasma insulin concentration at the end of the steady-state phase, and the insulin sensitivity index are shown.

ham Study, have indicated a strong correlation between plasma fibrinogen and subsequent myocardial infarction or stroke.[22-24] Fibrinogen has also been shown to be related to the severity of angiographically determined atherosclerosis[25] and inversely correlated with the patency of coronary bypass grafts.[26] During a 2-year follow-up study of 3,043 patients with angina pectoris, an elevated plasma fibrinogen concentration, even within the normal range, was found to be a strong independent predictor of subsequent acute coronary disease. In addition, a low fibrinogen concentration characterized patients with a low risk for coronary events despite elevated serum cholesterol.[24]

It has been suggested that fibrinogen may normally be eliminated by uptake in endothelial cells or pericapillary histiocytes,[27] a process that may be facilitated by the effect of α-blockers on precapillary sphincter muscles. The decrease in plasma fibrinogen in atenolol-treated patients in the present study is of a magnitude similar to that previously reported for celiprolol (−12%) but less pronounced than that noted for propranolol (−22%), both observations in studies on the treatment of essential hypertension.[28,29] Since hematocrits were unaffected in both treatment groups, the possibility of hemodilution/hemoconcentration as a reason for the changes in plasma fibrinogen concentrations seems less likely.

PAI activity, which also has been found to be a predictor of the progress of coronary atherosclerotic disease,[30,31] increased during atenolol treatment by 17% and decreased during urapidil treatment by 4%. These changes are not significant, and are in accordance with the previously reported absence of significant differences in PAI activity between mildly hypertensive patients treated with atenolol and those treated with the α-blocker, doxazosin.[32]

In conformity with previous observations, a correlation was found between PAI activity and fasting insulin and glucose levels, as well as TG.[33,34] In the present study, an inverse correlation was also observed between PAI activity and the insulin sensitivity index. However, in accordance with previous reports, the significant correlation between PAI activity and insulin resistance disappeared after adjusting for VLDL TG.[35,36] It has been proposed that an increase in VLDL may be associated with an increase in PAI activity via stimulation of the endothelial cells.[37] In addition, some findings indicate that VLDL from hypertriglyceridemic subjects enhances PAI synthesis more than VLDL from normotriglyceridemic subjects.[37] Thus, increased PAI activity may be a consequence of the atherothrombogenic syndrome including elevated lipid levels and hyperinsulinemia. The close correlation between plasma fibrinogen and PAI activity has previously been described, but the connecting mechanisms are still being debated.[38]

When the results were analyzed with regard to sex-related differences, PAI activity was found to be significantly reduced in urapidil-treated men, whereas women

showed a nonsignificant increase. The reason for this sex-related difference in the urapidil-treated subgroup remains to be explained, since there were no corresponding differences in other variables correlated with PAI activity, such as BMI, serum VLDL TG, or fasting plasma insulin. It should also be kept in mind that there were a limited number of treated subjects.

Urapidil treatment reduced VLDL TG concentration by 22% and total TG by 13%, but did not affect LDL cholesterol and total cholesterol levels. These findings are in line with previously reported results of prazosin and doxazosin treatment at this laboratory.

In three previous studies, no changes in lipoprotein status were observed during periods of 1 month to 3 years of urapidil treatment.[39-41] However, in a large-scale study of 5,454 elderly hypertensive patients receiving urapidil for an average of 3 months, LDL cholesterol and total cholesterol decreased by 10%, whereas HDL cholesterol increased by 12%.[42] In a retrospective analysis of six studies, Pattenier and von Heusinger[43] concluded that urapidil had no significant effects in patients with a normal or borderline-normal lipoprotein concentration, but caused a significant decrease in total cholesterol, LDL cholesterol, and total TG in patients with an abnormal lipoprotein status, which may help to explain the different reported effects on lipoprotein status. A dose-dependent reduction in total TG was noted when hypertensive patients with non–insulin-dependent diabetes mellitus were treated with urapidil.[44] The alteration in lipid status during urapidil treatment may be partly explained by the α-blocker–mediated increase in lipoprotein lipase activity, indicating improved TG disposal.[45-47] There seems to be either no difference or only a slight difference between α-blockers with and without 5HT1A receptor agonism with regard to effects on serum TG.[8,10]

In the atenolol-treated group, VLDL TG, LDL TG, and total TG increased, whereas HDL cholesterol showed a tendency to decrease. These changes, which could be a result of a decreased capacity for TG disposal, are similar to those reported in previous studies.[7,48]

During the hyperinsulinemic-euglycemic clamp test, urapidil treatment caused an improvement in glucose disposal (10%, NS). After adjustment for the prevailing insulin concentration during the steady-state phase of the clamp, the insulin sensitivity index showed a small increase (4%, NS). These results may be compared with the results of treatment using other antihypertensive drugs. Prazosin or doxazosin improved the insulin sensitivity index by +20%,[11,49] and captopril by +18%.[8] These are so far the only drugs studied at our laboratory that have significantly improved insulin sensitivity. β-Blockers,[7] but not dilevalol[50] diuretics such as hydrochlorothiazide[8] and bendrofluazide,[51] and also the calcium antagonist, nifedipine,[52] impair insulin sensitivity significantly.

In the present study, there were no significant changes in $AUC_{glucose}$ or $AUC_{insulin}$ at the OGTT in patients treated with urapidil.

In accordance with previous studies,[39,40] fasting blood glucose, fasting plasma insulin, and HbA_{1c} did not change during antihypertensive treatment with urapidil, which also underlines the fact that the urapidil dose used in the present study does not impair glucose metabolism. Furthermore, in hypertensive type II diabetic patients, a decrease in fasting blood glucose and HbA_{1c} has been reported.[44]

In the present study, treatment with atenolol did not affect insulin sensitivity as evaluated by the hyperinsulinemic-euglycemic clamp. This contrasts with our previous results of four studies on atenolol, which decreased the insulin sensitivity index by 13% to 23%.[7,49,53,54] In the previous studies, there was a significant inverse relationship between the pretreatment M/I ratio and the change in the M/I ratio during atenolol treatment,[55] and atenolol-treated patients in the present study had a low M/I ratio during the initial placebo period. Fasting plasma glucose and insulin levels did not change. However, HbA_{1c} increased by 4%, but the change was nonsignificant.

The study medication was withdrawn in five patients treated with urapidil due to insufficient reduction of blood pressure or negative side effects such as tiredness, headache, nasal congestion, or urinary incontinence. On the other hand, at least two men on urapidil treatment spontaneously commended the study drug because of easier voiding. One urapidil-treated man experienced two different side effects: slight nasal congestion and improved erection. These side effects have also been reported previously during treatment with α-blockers.[56]

In conclusion, the present study showed few statistically significant differences between the effects of urapidil and atenolol on metabolic variables. When summarizing the tendencies and significant changes in the two drug-treated groups, urapidil treatment may be characterized as having neutral or favorable effects on several metabolic variables associated with the atherothrombogenic syndrome. Atenolol treatment showed neutral properties in some metabolic aspects, but had deleterious effects regarding lipoprotein fractions associated with atherothrombogenic conditions.

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