α_1-Blocker Doxazosin Improves Peripheral Insulin Sensitivity in Diabetic Hypertensive Patients

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The antihypertensive doxazosin is a selective α_1-adrenoceptor–blocking drug whose favorable impact on lipid metabolism is well known. A single-blind placebo-controlled crossover study was designed to determine whether antihypertensive treatment with doxazosin affects insulin sensitivity in diabetic, mildly hypertensive, non-obese patients. Twelve subjects (diastolic blood pressure, 98 ± 1.5 mm Hg; body mass index, 25 ± 0.6 kg/m^2; hemoglobin A_{1c} [HbA_{1c}], 7.6% ± 0.4%) who were not taking drugs and were treating diabetes only by diet were randomly assigned to placebo treatment for 6 weeks and then to doxazosin for the same period, or vice versa. The doxazosin dose (maximum, 12 mg/d) was increased to achieve a normotensive blood pressure (final diastolic pressure, 85 ± 2 mm Hg, $P < .05$). A euglycemic (100 ± 4 mg/dL) hyperinsulinemic (61 ± 6 μU/mL) glucose clamp was performed at baseline and at the end of both placebo and doxazosin administration. Hepatic glucose production was measured by the isotope dilution technique using ^{3}H-glucose. Body weights and HbA_{1c} did not vary during the entire study. The basal mean glucose uptake and the insulin sensitivity index (2.3 ± 0.3 mg/kg/min and 4 ± 0.5 mg/kg/min per U/L × 100) remained unchanged during placebo administration (2.5 ± 0.4 and 4 ± 0.6, NS), but significantly increased during doxazosin treatment (3.3 ± 0.4 and 5.6 ± 0.7, $P < .05$). Hepatic glucose production showed no modification during both placebo and doxazosin. These data provide evidence that doxazosin improves insulin sensitivity in diabetic hypertensive patients, mainly through peripheral effects.

IT IS WELL KNOWN THAT in essential hypertension, even lean subjects with normal glucose tolerance present with an insulin-resistant state,[1] often with compensatory hyperinsulinism. Even if insulin resistance is only an epiphenomenon of the dysmetabolism secondary to hypertension, it could be responsible for the increased atherogenesis that characterizes the disease. This hypothesis fits well with some widely accepted epidemiologic observations showing that antihypertensive treatment is more effective in reducing strokes than coronary events.[2] This finding may be explained by the adverse impact of antihypertensive agents used in the trials on insulin sensitivity, which affects coronary risk, whereas decreasing blood pressure is the overriding mechanism by which stroke risk is reduced.

Nowadays, simply controlling the hemodynamic effects, which is essential for prevention of strokes and heart failure, is not considered enough for an antihypertensive drug to be judged optimal. There is growing concern about the metabolic effects of antihypertensive agents.

According to previous studies, in terms of clinical interest, the α_1-adrenoceptor inhibitors are the most important lipid-lowering antihypertensive drugs.[3] Their valuable effect on insulin action has been shown recently in essential hypertension with both normal glucose tolerance[4,5] and overt diabetes.[6,7]

In this regard, it was considered of clinical interest to confirm the effect of doxazosin on insulin sensitivity by using accurate methods in subjects who present with a state of severe insulin resistance, such as hypertensive non–insulin-dependent diabetic patients. The main aim was to determine the site of this effect, ie, peripheral or hepatic.

SUBJECTS AND METHODS

Patient Characteristics

Twelve diabetic patients (seven men, five women) suffering from untreated mild hypertension (diastolic pressure, 98 ± 1.5 mm Hg) were recruited for the study from a Northern Italy diabetic outpatient clinic (USSL 30, Chieri, Italy). The diagnosis of diabetes had been previously made by performing a 75-g oral glucose tolerance test. Only patients with no other previous or concomitant diseases who were taking no treatment in the previous 2 months were included. Renal failure (serum creatinine > 1.0 mg/dL, uric acid > 8 mg/dL) and cardiovascular (abnormal electrocardiogram) and retinal (abnormal fundus oculi) complications were grounds for exclusion from the study. The patients' main characteristics were as follows: age, 58 ± 2.2 years; weight, 69.5 ± 2.6 kg; and body mass index, 25 ± 0.6 kg/m^2. They were in good metabolic control (hemoglobin A_{1c} [HbA_{1c}], 7.6% ± 0.4%) and were treating diabetes only by diet.

Oral consent was obtained at the time of patient selection.

Study Design

Patients were asked not to change their diets and not to vary their physical activity. They were randomly assigned to placebo treatment for 6 weeks and then to doxazosin for the same period, or vice versa (single-blind crossover design). The dosage of doxazosin (maximum, 12 mg/d) was increased every 2 weeks to achieve a normotensive blood pressure (final diastolic pressure, 85 ± 2.1 mm Hg).

Blood pressure was measured according to World Health Organization criteria,[8] and the average of two readings was used.

Insulin Sensitivity Assessment

The most sensitive method to measure insulin sensitivity is the glucose clamp technique,[9] which, combined with the study of glucose hepatic production by ^{3}H-glucose infusion,[10-13] provides information about the site of insulin sensitivity variations. A euglycemic hyperinsulinemic glucose clamp, in addition to several laboratory tests, was performed at baseline and at the end of

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placebo and doxazosin administration. The technique has been described in detail.[9] The rate of insulin infusion (Actrapid; Novo, Copenhagen, Denmark) was 30 mU/m^2/min in all subjects, which resulted in a mean plasma insulin concentration of 61 ± 6 mU/L. The chosen plasma glucose concentration during the clamp study was 100 ± 4 mg/dL, and there were no significant changes in the coefficient of variation between different treatment periods.

Blood glucose level was measured every minute by means of an artificial pancreas.[14] Blood samples for determining insulin dosage were drawn at 100, 110, and 120 minutes of the clamp study. Steady-state plasma glucose and plasma insulin concentrations were calculated as the mean of values obtained between 100 and 120 minutes of the clamp study. The amount of glucose taken up (mg/kg/min) was used as the main target variable for that individual study. The insulin sensitivity index, a measure of the sensitivity of tissue to insulin expressed per unit of insulin, was calculated by dividing the amount of glucose taken up by the mean insulin concentration during the same period of the clamp.[9]

Hepatic glucose production was measured by the isotope dilution technique using ^{3}H-glucose (specific activity, 7.8 Ci/mmol; Amersham International, Amersham, Bucks, UK) administered as a primed-constant (0.25 μCi/min) infusion for 120 minutes. The bolus dose was 0.25 μCi. Blood samples for determination of ^{3}H-glucose specific activity were obtained at 10-minute intervals during the final 30 minutes. Basal hepatic glucose production was calculated according to the modified Steele equation.[10,11]

Statistical Analysis

The Wilcoxon signed-rank test was performed for the statistical analysis of results. A P value of less than .05 was considered significant. The statistical package used for calculations was Statistix Version 1.0 (N.H. Analytical Software, USA).

RESULTS

All results are expressed as the mean ± SEM. One woman dropped out of the study during treatment with doxazosin at a dose of 4 mg/d because of urinary incontinence as a side effect. This phenomenon, although unpleasant, was not surprising, since α_1-blockers have been proposed in the treatment of benign prostatic hypertrophy to relieve obstructive symptoms.[3]

Mean body weight did not vary during the entire study; only one patient gained weight abnormally between baseline and the end of treatment with doxazosin (+4 kg). No statistically significant variations in HbA_{1c} were found during the study (basal, 7.6% ± 0.4%; during placebo, 8.2% ± 1%; and during doxazosin, 8.1% ± 1%; P = NS, all comparisons). Fasting blood glucose was likewise unchanged: 100 ± 3.8 mg/dL at baseline, 101 ± 3.6 during placebo, and 100 ± 3.7 during doxazosin.

Basal mean glucose uptake and the insulin sensitivity index (2.3 ± 0.3 mg/kg/min and 4 ± 0.5 mg/kg/min per mU/L × 100) remained unchanged during placebo (2.5 ± 0.4 and 4 ± 0.6, NS), but significantly increased during doxazosin (3.3 ± 0.4 and 5.6 ± 0.7, $P < .05$). These data are presented in Fig 1.

Basal hepatic glucose production was 2.2 ± 0.5 mg/min/kg at baseline, 2 ± 0.3 during placebo, and 1.9 ± 0.3 during doxazosin (NS, all comparisons).

Residual glucose production (ie, hepatic glucose production during the final 20 minutes of the clamp steady state) was 1.2 ± 0.30 mg/min/kg at baseline, 1.3 ± 0.27 during placebo, and 1.6 ± 0.27 during doxazosin (NS, all comparisons).

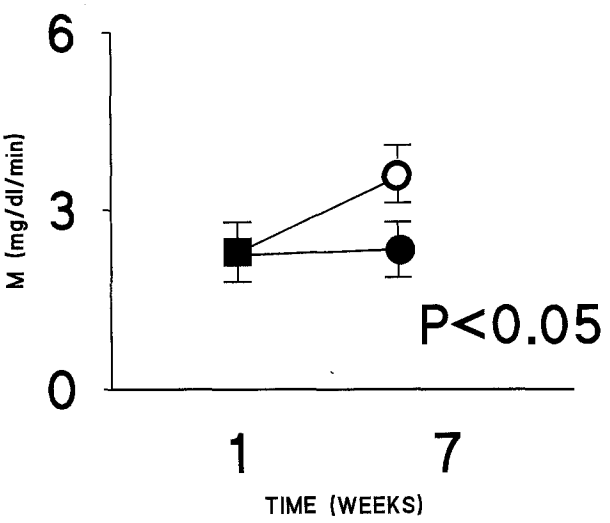

Fig 1. Mean glucose uptake (M) at baseline (■), during placebo (●), and during doxazosin (○).

All lipid values are listed in Table 1. Apolipoprotein A1 (131 ± 8 mg/dL baseline *v* 128 ± 14 during doxazosin *v* 117 ± 14 during placebo), apolipoprotein B (142 ± 11 mg/dL *v* 141 ± 12 *v* 111 ± 10), and nonesterified fatty acids (0.58 ± 0.1 mg/dL *v* 0.6 ± 0.1 *v* 0.6 ± 0.2) showed no significant variation.

No modification was found regarding other laboratory tests for parameters such as creatinine, liver enzymes, bilirubin, and fibrinogen, whose normal basal values did not vary throughout the study.

DISCUSSION

These data provide evidence that doxazosin improves insulin sensitivity in diabetic hypertensive patients. Since they were obtained using the most accurate method, ie, a crossover placebo-controlled trial with a euglycemic clamp to assess insulin sensitivity, they confirm previous observations[6,7] beyond doubt.

It is noteworthy that the patient who gained weight was the only subject who did not show any improvement in glucose uptake. The best explanation for this case is that

Table 1. Lipid Profiles at Baseline, During Doxazosin, and During Placebo

	Baseline	Doxazosin	Placebo
TC (mg/dL)	182.3 ± 10.1	192.4 ± 9.0	192.6 ± 10.4
LDL (mg/dL)	101.2 ± 8.2	116.7 ± 7.8	123.2 ± 13.4
HDL (mg/dL)	41.4 ± 3.6	42.3 ± 3.6	41.6 ± 4.0
TG (mg/dL)	181.7 ± 16.8	192.4 ± 9.0	192.6 ± 10.4
TC/HDL	4.6 ± 0.4	4.9 ± 0.5	5.0 ± 0.5

NOTE. All comparisons are statistically nonsignificant.

Abbreviations: TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides.

the adverse metabolic effect of weight gain prevailed over the effects of the drug.

No other interference capable of affecting insulin sensitivity can be claimed, since physical activity, type of diet, and the degree of metabolic control as measured by HbA_{1c} levels were unchanged during the entire trial.

In essential-hypertensive nondiabetic patients, prazosin was shown to increase glucose disposal by 30%.[4] Our findings support the hypothesis that doxazosin, which is as effective as prazosin as an antihypertensive but has fewer side effects, has similar favorable effects on insulin action. The magnitude of this improvement in insulin sensitivity, as measured by the euglycemic insulin clamp technique, is the greatest ever shown during an antihypertensive treatment. Some angiotensin-converting enzyme inhibitors were also found to have favorable effects on insulin action, but the size of these effects is smaller.[15] Recently, a similar marked increase in insulin action, approximately 30%, has been shown after treatment with celiprolol.[16] This compound shares vasodilating properties with doxazosin, although it is basically a β_1-blocker and β_2-agonist.

It has been suggested that the degree of vasodilation of skeletal muscle arteriolae may play a key role in the development of insulin resistance in hypertension and possibly type II diabetes.[17] Consequently, the capacity of some antihypertensive compounds to ameliorate insulin sensitivity may be due to vasodilating properties, which increase blood flow in the muscle, thereby expanding the proportion of tissue that comes into contact with insulin. Since our data show that during doxazosin therapy hepatic glucose production remains unchanged, they can be considered an important clue to this theory, ie, α_1-blockers improve insulin sensitivity mainly through peripheral effects. To our knowledge, this is the first time that the effects of α_1-blockers on insulin action have been investigated while taking into account hepatic glucose production. Other investigators[7] have wondered if α_1-blocking drugs might interfere with hepatic glucose production—our findings have enabled us to rule out the liver and to state that peripheral action (and possibly blood flow) is the correct area for research.

As for other parameters of metabolic interest, such as the lipid and lipoprotein profiles listed in Table 1, it is noteworthy that no significant modification was found. Since our group had previously experienced the effective lipid-lowering action of doxazosin over a 6-month period,[5] this result was rather unexpected. However, all the investigators reported these effects over longer periods, that is, never less than 12 weeks, and moreover, on patients with worse lipid profiles at baseline.[18,19] A similar lack of effect on total cholesterol and triglyceride levels had already been shown after a brief treatment in diabetic subjects in a previous study of doxazosin.[20] In our trial, the brief period of treatment, as well as the almost-normal lipid levels of the patients, may have blunted the lipid-lowering properties of the compound.

The brief period of treatment may also explain why HbA_{1c} did not vary after doxazosin treatment, although there was a marked increase in insulin sensitivity.

As for HbA_{1c} and glucometabolic control, it is also worth noting that, due to the lack of effect on hepatic glucose production, fasting glucose levels did not vary in the same way. The latter may be a further reason why HbA_{1c} levels were not affected.

In conclusion, our observations provide two important clinical implications: (1) Doxazosin may be proposed for the treatment of hypertension when the least interference with glucose metabolism is needed, namely in insulin-resistant states such as type II diabetes; and (2) Doxazosin positively affects at least two risk factors for coronary artery disease at the same time—hypertension and insulin resistance.

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