A Double Blind Comparison of the Effects of Amlodipine and Enalapril on Insulin Sensitivity in Hypertensive Patients

Dan Lender, Carlos Arauz-Pacheco, Laura Breen, Pablo Mora-Mora, Luis C. Ramirez, and Philip Raskin

This study compares the effects of a calcium channel blocker (amlodipine) and an angiotensin converting enzyme inhibitor (enalapril) on in vivo insulin sensitivity in patients with essential hypertension. Forty-six patients with mild and moderate hypertension were studied. After a 2-week single-blind placebo phase, they were randomly assigned to double-blind therapy with either amlodipine (2.5 to 10 mg/day) or enalapril (5 to 40 mg/day) for 16 weeks. Both groups were comparable in terms of demographic characteristics, degree of obesity, metabolic parameters, and arterial blood pressure. Insulin sensitivity was measured at baseline and at week 16 during the active phase using euglycemic hyperinsulinemic clamps. Arterial blood pressure decreased similarly in both groups. Whole body glucose uptake (M-value) increased with amlodipine from $3.63 \pm 0.32$ (mean ± SEM) to $3.97 \pm 0.31$ mg/kg/min ($P = .02$). A similar tendency was observed with enalapril: from $3.59 \pm 0.32$ to $3.94 \pm 0.30$ mg/kg/min ($P = .09$). A trend to lower steady-state insulin level during the second clamp (compared to baseline) was observed in both groups. The clamp-derived insulin sensitivity index (that corrects for steady-state insulin levels and glucose levels during the clamp) increased similarly in both groups: from $1.15 \pm 0.11$ to $1.39 \pm 0.13$ with amlodipine ($P = .03$) and from $1.25 \pm 0.13$ to $1.49 \pm 0.16$ with enalapril ($P = .01$). LDL cholesterol decreased with amlodipine (mean change, $-11.3$ mg/dL, $P = .004$). Amlodipine and enalapril were associated with increments in insulin sensitivity. Amlodipine provided an additional benefit with decreased low density lipoprotein cholesterol levels. — Am J Hypertens 1999;12:298–303 © 1999 American Journal of Hypertension, Ltd.

Key words: Calcium channel blocker, amlodipine, angiotensin converting enzyme inhibitor, enalapril, insulin sensitivity.
β-blocker responses have been shown to further decrease the metabolic responses to insulin (insulin-mediated glucose uptake)\(^6,^7\) and this may explain their effects on lipid and glucose levels. α-Adrenergic blockers and angiotensin converting enzyme (ACE) inhibitors have been reported in some,\(^7–^9\) but not in all, studies\(^10,^11\) to increase insulin-mediated glucose uptake. These effects may have a theoretical advantage if insulin resistance proves to be a deleterious factor on cardiovascular disease. The studies using the calcium channel blocker (CCB) family of drugs have been conflicting. Studies in dogs by Hirayama et al\(^12\) suggest a positive effect on insulin sensitivity of nicardipine, a dihydropyridine calcium channel blocker. Also reports suggest that amlodipine is associated with a decrease in LDL cholesterol levels\(^13\) and an increase in insulin sensitivity in essential hypertension.\(^14\) No double-blind studies comparing the effects of calcium channel blockers and ACE inhibitors on insulin sensitivity in essential hypertension have been published.

This study was designed to evaluate the effects of enalapril, an ACE inhibitor, and amlodipine, a CCB of the dihydropyridine group, on insulin-mediated glucose uptake and lipid parameters in subjects with essential hypertension. We tested the hypothesis that amlodipine would have a positive effect on insulin sensitivity similar to the effect previously reported with ACE inhibitors.

**PATIENTS AND METHODS**

This was a randomized, double-blind, parallel study to compare the effects of amlodipine on glucose metabolism and insulin sensitivity in patients with mild to moderate hypertension. The study was approved by the Institutional Review Board at the University of Texas Southwestern Medical Center at Dallas. All participants gave written consent after being informed of the nature and risks involved in the study. Fifty adult patients of either gender with mild to moderate essential hypertension were randomized equally to receive either amlodipine or enalapril for 16 weeks. All previous antihypertensive medications were discontinued at least 2 weeks before entering the study. During the first phase of the study, patients were given placebo in a single-blind fashion to evaluate compliance and stability of the blood pressure levels. Inclusion criteria for randomization were 1) a sitting diastolic blood pressure between 95 and 114 mm Hg for 2 weeks while the patients received placebo; 2) absence of diabetes mellitus as determined by fasting blood glucose level < 140 mg/dL; and 3) absence of any acute or severe chronic cardiovascular, hepatic, or renal disease at the time of screening. Patients who qualified during the single-blind placebo phase were randomized to receive enalapril 5 mg orally per day or amlodipine 2.5 mg orally per day, in a double-blind fashion. During the initial 8 weeks of the double-blind phase, the drug dosages were titrated to obtain adequate blood pressure control defined as a sitting diastolic blood pressure < 90 mm Hg or a decrease in sitting diastolic blood pressure > 10 mm Hg or until the maximum dose of the study drugs was achieved (10 mg/day for amlodipine and 40 mg/day for enalapril). After the end of the titration period, the drugs were continued at a stable dose for the remaining 8 weeks of the study. During the duration of the study, patients were instructed not to change their dietary habits or weight, and to maintain the same activity levels compared to baseline.

The day before randomization, patients underwent the following laboratory studies: fasting plasma glucose, fasting plasma insulin, fasting lipid levels (total cholesterol, triglycerides, HDL cholesterol, very low density lipoprotein (VLDL) cholesterol by ultracentrifugation, and LDL cholesterol obtained with the formula: LDL cholesterol = Total cholesterol – (VLDL cholesterol + HDL cholesterol). Percent of body fat was obtained from body density measurements using underwater weighing. The following day patients were admitted to the General Clinical Research Center at Parkland Hospital for the performance of an initial euglycemic clamp study. This was performed as described by DeFronzo et al.\(^15\) A primed-continuous insulin infusion was administered using a 2205 Harvard Apparatus Infusion Pump (Holliston, MA). The continuous infusion rate was set at 40 mU/m\(^2\) (body surface area)/min during 2 hours. Eighteen percent glucose was infused at a variable rate according to the plasma glucose level measured every 5 min to maintain a steady plasma glucose at baseline level. Insulin sensitivity was calculated from the glucose infusion rate and the plasma glucose and insulin levels during the last 30 min of the clamp and expressed in milligrams of glucose/kilogram of fat-free mass/minute (M-value) and also as a clamp-derived insulin sensitivity index\(^16\) to correct for insulin and glucose levels during the clamp, and obtained with the following formula: insulin sensitivity index = glucose disposal rate (mg/kg/min)/steady-state insulin × steady-state glucose. After the metabolic study, the double-blind phase of the study began. At the end of 16 weeks on double-blind medication, the same studies were repeated while the patients were taking the maintenance dose of study drugs.

**Statistical Analysis** Efficacy measures in this study fall into three categories: The first category was cardiovascular measures, these include sitting and standing systolic and diastolic blood pressure and heart rate. These were measured at screening, every week during the initial placebo phase and every 2 weeks thereafter. The mean of two measurements during
each visit was used in the analysis. A second category of measures involved glucose and insulin measurements, and insulin sensitivity measurements. These were taken at randomization and at the end of the double-blind phase. The third category included the lipid parameters measured at randomization and at the end of the titration phase and at the end of the double-blind phase. Data are presented as means ± SEM. The analysis of the blood pressure and lipid data was performed using analysis of covariance methods. The data were first to fit to a model that included treatment group, baseline, and baseline by treatment interaction. If baseline by treatment was not statistically significant it was removed from the model and inference based on the reduced model. The response in the model was the on-therapy value minus baseline. Least square means were used to estimate treatment effects. The insulin sensitivity measures were compared using the Student’s t test for paired observations. A .05 significance level was used.

RESULTS

Forty-six patients completed the double-blind phase of the study, one patient in the amlodipine group dropped out due to intercurrent illness before any therapy evaluation was done. Three enalapril patients failed to complete the study, in two the cause of discontinuation was adverse events and in one, the cause was inadequate response to therapy. The cardiovascular results available for these patients are included in the analysis. Because these patients did not undergo the second clamp study, the metabolic data are not available. The baseline characteristics of the study patients are shown in Table 1. Four patients in the amlodipine group and three in the enalapril group had fasting plasma glucose levels >110 and <126 mg/dL at baseline, considered impaired fasting glucose according to the recent diabetes classification. One additional patient in the amlodipine group had a fasting plasma glucose of 126 mg/dL, considered diabetic according to the new classification.17 Four of the seven patients with abnormal fasting glucose at baseline had normal fasting glucose levels in the final evaluation (two in each group).

Weight did not change significantly in any of the study groups [body mass index (BMI) 27.9 ± 0.8 v 28.0 ± 0.8 (amlodipine group, baseline versus week 18) and 29.0 ± 0.7 v 29.1 ± 0.8 (enalapril baseline v week 18)]. At the doses used, both amlodipine and enalapril groups had decreased blood pressure levels to a similar degree (Table 2). A slightly greater decrease in diastolic blood pressure was seen with amlodipine. The statistical significance of this difference was borderline (P = .06). The mean dose of enalapril was 28.3 ± 8.6 mg/day and that of amlodipine was 8.6 ± 3.3 mg/day. During the clamp studies, glucose was maintained at a level of 5.7 ± 0.2 mmol (103 ± 4 mg/dL) and 5.6 ± 0.2 mmol (101 ± 4 mg/dL) on the first and second studies. Insulin levels achieved during the clamps were 832 ± 39 pmol and 755 ± 30 pmol in baseline and final study, respectively (P < .05).

In spite of a tendency to lower steady-state insulin levels with both drugs during the treatment phase, the whole body glucose uptake (M-value) increased significantly with amlodipine (P = .02), and a similar trend was observed with enalapril (P = .09) (Figure 1a). The clamp-derived insulin-sensitivity index increased with both drugs by an average of 20% (Figure 1b).

No significant correlation was found between the

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<th>TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY SUBJECTS</th>
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SBP, systolic blood pressure (mm Hg); DBP, diastolic blood pressure (mm Hg).

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<th>TABLE 2. HEMODYNAMIC EFFECTS (CHANGES V BASELINE) OF AMLODIPINE AND ENALAPRIL</th>
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SBP, systolic blood pressure (mm Hg); DBP, diastolic blood pressure (mm Hg).
LDL cholesterol levels were decreased by 11.3 mg in the amlodipine group \( (P = .04) \). No significant changes in lipid levels were observed with enalapril. No changes were observed in triglycerides, HDL, or VLDL with any of the study drugs (Table 3).

**DISCUSSION**

This study shows evidence that antihypertensive drugs of the calcium channel blocker and the ACE inhibitor groups increase insulin-mediated glucose uptake in subjects with essential hypertension. The group of patients studied consisted of moderately obese individuals with a mean BMI of 28.5 and a mean body fat content of 30.5. This degree of obesity has been associated with insulin resistance in several studies. Essential hypertension has been associated with insulin resistance independently of obesity.

In a separate report by our group, the insulin sensitivity of the subjects included in this publication was compared to a group of normotensive subjects matched for age, weight, and percent of body fat and a significant degree of insulin resistance was found in the hypertensive group, indicating that there is a component of the insulin resistance in this group of patients that is independent of the degree of obesity.

We found no significant correlation between the antihypertensive response and the increase in insulin sensitivity suggesting that the effects of the drugs is not directly related in their hemodynamic effects. We did not find a correlation between baseline blood pressure levels and baseline insulin sensitivity. This is explained by the selection process in which only patients within an elevated blood pressure were included, not allowing comparisons between a wide range of blood pressure levels.

The clinical relevance of this effect is unknown, but based on the studies showing that insulin resistance and compensatory hyperinsulinemia may impose an increased atherogenic risk, interventions that decrease insulin resistance would have theoretical advantages.

In addition, amlodipine was associated with a beneficial effect on total cholesterol and LDL cholesterol levels. We did not measure postprandial insulin levels.
in this study, therefore the effects of the drugs on postprandial hyperinsulinemia are not known.

Calcium channel blockers and ACE inhibitors have different mechanisms of action on the blood pressure levels. The mechanisms by which these drugs exert their metabolic effects are only speculative. It is unknown whether common pathways are involved. Both drugs decrease peripheral vascular resistance and produce vasodilation. Because insulin-mediated glucose uptake during euglycemic clamps occurs mostly (80% to 90%) in skeletal muscular tissue, and is dependent on muscular blood flow, an increase in blood flow induced by vasodilatory drugs, could theoretically increase glucose uptake. Studies by Hall et al suggest, however, that marked changes in muscular blood flow produce only minor changes in vivo insulin sensitivity. ACE inhibitors produce elevation in bradykinin levels, as ACE is identical to kininase II. Bradykinin can induce muscular vasodilation and also increase glycolytic flux. Rett et al have presented evidence that ACE inhibitors and bradykinin are capable of markedly increasing muscular glucose uptake. The effects of calcium channel blockers could theoretically be produced by decreasing intracellular Ca*2+ in the smooth muscle cell and inducing vasodilation. Insulin has a vasodilatory effect on the skeletal muscle and insulin-resistant states are associated with decreased insulin-induced vasodilation. Insulin has been shown to activate cell membrane Na+,K+-ATPase and Ca*2+-ATPase in the smooth muscle cell, and also decrease Ca*2+ influx through voltage and receptor-operated channels, thereby resulting in decreased intracellular calcium levels. Insulin resistance has been associated with blunting of these functions resulting in increased intracellular Ca*2+ levels. The administration of CCB may result in a restoration of insulin-mediated vasodilation by decreasing intracellular Ca*2+ levels, and the increased muscular perfusion would result in increased glucose disposal and may explain the effects observed in this study and in a previous report. High intracellular Ca*2+ has also been associated with insulin resistance indicating a potential metabolic site for CCB action to increase insulin action.

LDL cholesterol levels were lower after therapy with amlodipine in this study. This contrasts with the adverse lipid profile frequently observed with diuretic and β-adrenergic blockers. Other studies have reported a neutral or beneficial effect of calcium channel blockers on lipid levels. Calcium channel blockers at concentrations within the range required to lower blood pressure may inhibit the expression of 3-hydroxy-3-methylglutaryl-coenzyme A reductase gene and induce the LDL receptor gene in skin fibroblasts. If these mechanisms were operative in this study and resulted in the lower LDL levels is only speculative, but consistent with the observed results.

**REFERENCES**


