Metabolic Effects of Isradipine Versus Hydrochlorothiazide in Diabetes Mellitus

Renate Klauser, Rudolf Prager, Susanne Gaube, Christoph Gisinger, Christoph Schnack, Elisabeth Küienburg, Guntram Schernthaner

Most antihypertensive drugs have negative effects on metabolic control in diabetic patients. Calcium antagonists have been widely used in antihypertensive treatment of diabetics, although a possible influence on glucose tolerance, insulin secretion, and insulin action is unknown. Therefore, the effect of the calcium antagonist isradipine on glucose tolerance and insulin secretion (75 g oral glucose tolerance test) and on peripheral and hepatic insulin action (euglycemic clamp) was evaluated in 11 type II diabetic patients. All patients were treated with placebo or isradipine for 8 weeks (double-blind, crossover design). A second group of six diabetic patients received a thiazide diuretic, hydrochlorothiazide, according to the same protocol. Systolic blood pressure was significantly lowered after isradipine and hydrochlorothiazide compared with placebo (127±3 versus 139±6 mm Hg and 129±4 versus 142±4, respectively; p<0.05). Fasting blood glucose (190±21 versus 152±15 mg/dl; p<0.01), glucose levels, basal and glucose-stimulated insulin levels were significantly higher after hydrochlorothiazide compared with placebo but remained unchanged after calcium antagonist treatment. Basal hepatic glucose production and peripheral insulin resistance were significantly elevated after hydrochlorothiazide compared with placebo or calcium antagonist therapy. These data indicate that the calcium antagonist isradipine has no effect on glucose tolerance, insulin secretion, and insulin action in type II diabetic patients and might therefore be a useful drug for antihypertensive treatment in diabetes mellitus. However, diuretic treatment can lead to impairment of metabolic control and reduction of insulin action in type II diabetes mellitus. (Hypertension 1991;17:15-21)

Hypertension and diabetes mellitus are both common disorders in developed countries. In diabetic patients reduction of blood pressure has been shown to be beneficial and to reduce secondary late complications of diabetes mellitus.1,2 However, most antihypertensive drugs such as thiazide diuretics or β-blocking agents have adverse effects on metabolic control and on glucose counter-regulation in diabetic patients.3–6 In the past calcium antagonists have been increasingly used in the treatment of hypertension.7,8 Because calcium plays an essential role in hormone metabolism and especially in carbohydrate homeostasis and glucose-induced insulin secretion,9–11 calcium channel blocking agents might also interfere with metabolic control.12,13 Data from in vitro studies,10,14 animal studies,15,16 and humans with insulinomas17,18 suggest that calcium antagonists may increase serum glucose levels. A variety of in vivo studies concerning metabolic effects of calcium antagonists in diabetic12,13,19–23 and nondiabetic patients13,20,24–28 exists although most of them are short-term or not placebo-controlled studies. Furthermore, no data is available on peripheral and hepatic insulin action after calcium antagonist treatment—both parameters representing major metabolic abnormalities in type II diabetic patients.29,30 Therefore, we investigated the influence of isradipine, a new calcium channel blocker, whose antihypertensive action has been recently described31–34 on glucose tolerance, insulin secretion, and peripheral and hepatic insulin action in 11 type II diabetic patients. Another group of six patients was treated with a thiazide diuretic, hydrochlorothiazide, and the same parameters were evaluated. We performed these studies using a placebo-controlled, double-blind, crossover study design in both groups over a period of 8 weeks.
Methods

We investigated non-insulin-dependent type II diabetic patients. The study was preceded by a washout period of 2 weeks. Previous antihypertensive treatment, if present, was terminated at the beginning of this period. During the washout period the patients received placebo tablets (1 tablet twice daily) with an appearance identical to that of the active drug. After the first 2 weeks, the patients were treated during two consecutive 4-week periods with isradipine and placebo (group A) or with hydrochlorothiazide and placebo (group B). Group A was treated with a forced titration schedule (1 tablet containing 5 or 10 mg isradipine twice daily during the first or second half of the treatment period). Group B received treatment with 1 tablet containing 25 mg hydrochlorothiazide twice daily continuously throughout the treatment period.

All patients were asked not to change their eating or exercise habits during the study. Oral hypoglycemic agents if necessary were administered at a constant dosage throughout the study. After each 4-week treatment period, a 75 g oral glucose tolerance test (OGTT) with evaluation of insulin secretion and glucose tolerance and a euglycemic clamp for evaluation of peripheral and hepatic insulin sensitivity on the days after the OGTT were performed.

Patients

Study groups A and B consisted of 11 and six type II diabetic patients, respectively. Twelve healthy volunteers served as control group for evaluation of insulin action. Clinical and metabolic characteristics of the subjects are summarized in Table 1. Stable metabolic control had been achieved by diet or by diet combined with oral hypoglycemic agents. Patients with unstable or insulin-dependent diabetes mellitus were not included in the study. Patients with secondary hypertension, coronary heart disease, or impaired renal function were also excluded. All patients attended clinic visits and examinations at the Medical Department II, University of Vienna, Austria. The studies were approved by the local ethics committee and all patients gave informed consent.

Materials

The calcium channel blocker isradipine PN 200-110, a dihydropyridine derivative (Venflon, Viggo, Helsingborg, Sweden)(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid 2-methyl 5-(1-methylethyl)-ester) and placebo tablets were supplied by Sandoz, Basel, Switzerland. The thiazide diuretic hydrochlorothiazide (Esidrix [6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazin-1,1,-dioxide) was purchased at Ciba-Geigy, Vienna, Austria. Regular human insulin (Novo, Bagsvard, Denmark) was used for insulin infusions during the euglycemic clamp. [3-3H]Glucose was purchased from New England Nuclear, Boston, Mass.

Diet

All subjects were placed on a weight-maintaining diet (32 kcal/kg/day) containing 50% carbohydrate, 20% protein, and 30% fat. All patients had started and were stabilized on this diet at least 48 hours before any studies were performed. Throughout the experiments the subjects remained in a supine position and abstained from eating, drinking, and smoking. Each test was carried out on a separate day at 8:00 AM after an overnight fast. Study medication was given at 7:00 AM.

Oral Glucose Tolerance Test

At the end of each 4-week treatment period (either placebo or isradipine or hydrochlorothiazide), the patients underwent a 75 g OGTT. Blood samples were drawn at 0, 30, 60, 90, 120, 150, and 180 minutes after oral glucose load to obtain glucose and insulin levels.

Euglycemic Clamp

The day after the OGTT the euglycemic clamp was performed. A Teflon catheter was inserted in the antecubital vein for infusion of substances. Blood samples were taken from a retrograde cannulated hand vein kept warm (70°C) by a heating pad to ensure arterialized of venous blood. This venflon was kept patent with a 0.9% solution of saline. Insulin sensitivity was assessed by the euglycemic clamp technique. In brief, after an equilibration

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Values given are mean±SEM. SBP, systolic blood pressure; DBP, diastolic blood pressure. Analysis of variance: *p<0.05 group A vs. controls and group B vs. controls.
period of 120 minutes for \([3^{-3}H]\)glucose a constant regular insulin infusion was administered at a rate of 120 milliunits/m²/min for 4 hours. During this time the plasma glucose concentration was held constant at euglycemia (90 mg/dl) by a variable infusion of 20% glucose. The coefficient of variation never exceeded 3%. Blood glucose levels were measured at 10-minute intervals throughout the study to enable appropriate adjustment of glucose infusion rate. Each study was conducted for 4 hours plus the equilibration period of 2 hours for \([3^{-3}H]\)glucose. The overall rate of glucose disposal was assessed isotopically as described below.

**Measurement of Glucose Turnover**

Glucose turnover rate was evaluated during the basal state and during hyperinsulinemia during the clamp by infusion of \([3^{-3}H]\)glucose in a primed continuous manner (initial bolus of 60 \(\mu\)Ci was followed by continuous infusion rate of 0.6 \(\mu\)Ci/min). After a 120-minute equilibration period, the clamp studies were begun and blood samples were obtained at 20-minute intervals for determination of glucose concentration and specific activity. The rate of glucose disappearance (RD) and the rate of glucose appearance (RA) were calculated with the Steele equation in the modified derivative form because the tracer exhibits non-steady-state kinetics under these conditions. The value of 0.65 was used as pool fraction. When the isotopically determined RD was less than the rate of glucose exogenously infused (GI), the glucose disposal rate was taken as GI corrected for the change in glucose pool size.

**Measurement of Hepatic Glucose Output**

During the basal state hepatic glucose output (HGO) is the only source of glucose; therefore, the basal RA equals basal HGO. During the clamp, the rate of HGO was calculated as the difference between RA and GI.

**Analytical Methods**

Blood for serum glucose determination was drawn and centrifuged immediately in a Beckman microfuge (Beckman Instruments, Palo Alto, Calif.). Glucose was measured by the glucose oxidase method with an automated glucose analyzer (Beckman). Blood for determination of glucose-specific activity was collected in lithium-heparin–treated tubes and put on ice immediately. After separation, all samples were stored at \(\sim\)20°C until analysis. Plasma for determination of glucose-specific activity was deproteinized with perchlorate; the supernatant was evaporated to dryness, redissolved in water and counted in aqueous counting solution scintillation fluid (Amersham Corp., Arlington Heights, Ill.).

**Data Analysis**

Glucose turnover data were calculated with the optimal segments method originally described by Finegood and Bergman. All data are mean\(\pm\)SEM unless otherwise stated. Statistical analysis was performed with Student's \(t\) test for paired data and analysis of variance (ANOVA) as appropriate.

**Results**

**Blood Pressure**

The mean systolic blood pressure with the patient in a sitting position was significantly lowered after isradipine therapy and after hydrochlorothiazide therapy compared with placebo (127\(\pm\)3 versus 139\(\pm\)6 mm Hg, \(p<0.05\) for isradipine and placebo, respectively; 129\(\pm\)4 versus 142\(\pm\)4 mm Hg, \(p<0.01\) for hydrochlorothiazide and placebo, respectively). Diastolic blood pressure was also lower after both therapies compared with placebo, although the difference did not reach statistical significance (isradipine, 80\(\pm\)2; hydrochlorothiazide, 81\(\pm\)2; placebo, 85\(\pm\)3 mm Hg, NS). There were no significant heart rate changes after either drug.

**Oral Glucose Tolerance Test, HbA1c**

The results of the OGTT (glucose tolerance and insulin secretion) of the two diabetic groups are included in Table 2. No significant changes were found in group A concerning fasting blood glucose, fasting serum insulin, the integrated glucose levels (area under the curve [AUC] of glucose levels) or the integrated insulin levels (AUC of insulin levels) during the OGTT after isradipine compared with placebo treatment (Figure 1). All patients exhibited diabetic glucose tolerance according to the criteria of the National Diabetes Data Group. In group B a significant deterioration of fasting glucose levels and glucose tolerance after thiazide therapy was observed. Insulin levels during the OGTT also increased significantly after treatment (Figure 1). The impairment in metabolic control in this group was also impressive in regard to the long-term parameter HbA1c (7.7\(\pm\)0.5 versus 6.4\(\pm\)1%; \(p<0.005\) for hydrochlorothiazide and placebo, respectively). All patients had normal serum potassium levels, which were slightly lowered after hydrochlorothiazide treatment but still within the normal range (4.6\(\pm\)0.3 versus 4.2\(\pm\)0.4 versus 4.5\(\pm\)0.4 mmol/l for placebo, hydrochlorothiazide, and isradipine, respectively; NS). In group A no change in HbA1c levels after isradipine or placebo was observable.

**Peripheral and Hepatic Insulin Sensitivity**

Diabetic patients versus controls. During the clamp studies steady-state insulin levels of 250 milliunits/l were achieved at both times and in all groups. Both diabetic groups exhibited significantly higher basal hepatic glucose production rate compared with the normal group (basal HGO: group A, 91\(\pm\)4 mg/m²/min; group B, 96\(\pm\)6 mg/m²/min; control group, 81\(\pm\)2 mg/m²/min; ANOVA, \(p<0.05\)), whereas hepatic glucose production was equally suppressed during the clamp in diabetics and controls, probably due to the high insulin levels during the euglycemic clamp.
Peripheral insulin resistance was present in all diabetic subjects; therefore insulin-mediated peripheral RD was significantly lower compared with the normal group (RD: group A, 251±24 mg/m²/min; group B, 265±34 mg/m²/min; controls, 324±25 mg/m²/min; ANOVA, \( p < 0.05 \)).

Group A (isradipine versus placebo). Isradipine therapy did not change basal hepatic glucose produc-
tion (basal HGO, 96±6 versus 91±4 mg/m²/min for isradipine and placebo, respectively; NS), suppression of HGO (suppressed HGO, 5±3 versus 7±3% of basal HGO for isradipine and placebo, respectively; NS), or peripheral insulin sensitivity (RD, 266±23 versus 251±24 mg/m²/min for isradipine and placebo, respectively; NS).

Group B (hydrochlorothiazide versus placebo). During treatment with thiazide as compared with placebo, peripheral insulin sensitivity decreased significantly (RD, 212±31 versus 265±34 mg/m²/min; p<0.01). Because basal glucose levels were significantly elevated after thiazide therapy compared with placebo treatment and since hepatic glucose production represents the main source for basal blood glucose levels, basal HGO was expected to be higher, also. Indeed, basal HGO rose from 95±5 mg/m²/min to 140±19 mg/m²/min, p<0.05, after hydrochlorothiazide therapy. Suppression of HGO remained unchanged during hydrochlorothiazide treatment (7±2 versus 6±1% of basal HGO; NS).

Discussion

One of the principal findings of this study was that the treatment with the calcium channel blocker isradipine in non-insulin-dependent diabetic patients had no disturbing influence on glucose homeostasis. In contrast, treatment with hydrochlorothiazide resulted in a significant deterioration of metabolic control and impairment of peripheral insulin sensitivity. In a study by Swislocki et al,3 thiazide diuretic alone or combined treatment with β-blocker actually showed aggravation of insulin resistance, glucose intolerance, and hyperinsulinemia associated with hypertension. However, this study was cross-sectional, and long-term effects of the mentioned drugs could not be evaluated. Pollare et al5 compared the effects of hydrochlorothiazide and captopril on glucose metabolism in hypertensive nondiabetics and provided evidence that hydrochlorothiazide increased basal insulin concentrations and the late insulin response to intravenous glucose. Furthermore, hydrochlorothiazide was shown to decrease insulin sensitivity and enhance concentration of total and low density cholesterol and triglycerides. One study by Prince et al39 in 10 type II diabetic patients showed no effect of 25 mg hydrochlorothiazide on glucose levels and insulin sensitivity over a 4-week period. The present study was initiated to address these issues and evaluate effects on glucose metabolism, insulin secretion, and insulin action under antihypertensive treatment with either the calcium channel blocker isradipine or the thiazide diuretic hydrochlorothiazide in diabetic patients. Hydrochlorothiazide appeared to increase insulin secretion—basal as well as glucose stimulated—and to decrease glucose tolerance. During steady-state, peripheral glucose uptake was significantly reduced under hydrochlorothiazide treatment. Basal hepatic glucose production rose significantly after diuretic therapy, whereas hepatic insulin sensitivity during hyperinsulinemia remained unchanged. The results of our study provided further evidence that thiazide diuretics cause impairment of glucose tolerance and insulin sensitivity—peripheral as well as basal hepatic sensitivity—and indicated that thiazide treatment is not beneficial for type II diabetic patients. These data confirm previous reports5-8 of impaired metabolic control in diabetic patients after thiazide treatment, although one study did not show this effect.39 Two major reasons might be responsible for the difference in the outcome of our study and that of Prince et al.39 First, the patients in Prince’s study were already less insulin sensitive during the placebo phase (glucose infusion during steady state, 2.3±0.8 mg/kg/min) compared with the patients in our study (glucose disposal steady state, 6±1 mg/kg/min). Therefore, a deterioration in insulin sensitivity might not have been seen. Second, substitution of potassium was performed in the study mentioned above. We did not substitute potassium since all patients had normal serum potassium levels, which were slightly lowered after hydrochlorothiazide treatment but still within the normal range (4.6±0.3 versus 4.2±0.4 mmol/l for placebo and hydrochlorothiazide, respectively; NS).

In contrast, fasting glucose levels and the glycosylated hemoglobin HbA₁c as well as glucose-induced insulin secretion and glucose tolerance remained unchanged after isradipine therapy. In some studies,12,18,19 elevation of glucose levels and decreased insulin secretion during an OGTT were described after short-term oral or high dose intravenous infusions of calcium channel blockers in healthy individuals. However, this has not been confirmed when insulin release was measured directly in the portal venous blood.20 Two short-term studies in non-insulin-dependent diabetic subjects even showed improvement of glucose tolerance during an OGTT,19,20 However, calcium antagonists may reduce insulin secretion in insulinoma patients, although these studies investigated only a very small number of patients.17,18

In type II diabetes mellitus peripheral and hepatic insulin resistance are major factors contributing to deranged glucose homeostasis.29,30 The effect of calcium channel blockers during long-term treatment on these parameters has not yet been evaluated in controlled studies in diabetic patients. We found that both peripheral insulin sensitivity and suppression of hepatic glucose production during the euglycemic clamp were not affected by isradipine treatment. Because calcium channel blockers are increasingly used in antihypertensive treatment in type II diabetes mellitus, the results of our study are of significant clinical relevance especially since most other antihypertensive agents such as diuretics or β-blockers have adverse effects on metabolic control and on glucose counterregulatory hormones.3-6

The diabetic population evaluated in our study showed slightly elevated blood pressure levels; however, slight elevations in blood pressure, although within the normal range, in diabetic patients could
cause progression of diabetic nephropathy. The blood pressure-lowering effect in our study was, therefore, less striking than in patients with highly elevated blood pressure levels. However, the therapeutic efficacy of isradipine has been shown elsewhere.31-34 With a dose of 10 mg isradipine daily, effective blood pressure reduction could be observed in 82% of hypertensive patients (diastolic blood pressure greater than 100 mm Hg).31 Therefore, we believe that with our study design we were able to evaluate possible effects of efficient isradipine treatment on metabolic parameters. However, we cannot exclude different results in patients with severe hypertension.

Further, long-term controlled studies have to prove clinical observations that other calcium antagonists do not alter metabolic control in diabetic patients. Since isradipine did not affect glucose tolerance, insulin secretion, and peripheral and hepatic insulin sensitivity, this calcium antagonist seems to be a useful drug for treatment of hypertension in type II diabetes mellitus. However, hydrochlorothiazide did not seem to be beneficial in antihypertensive treatment in diabetic patients because of negative effects on glucose tolerance and insulin sensitivity.

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References


**KEY WORDS** • calcium antagonists • diuretic therapy • antihypertensive agents • diabetes • insulin • glucose
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