Improvement of Insulin Sensitivity By a Long-Acting Nifedipine Preparation (Nifedipine-CR) in Patients With Essential Hypertension

Yuko Koyama, Kenichi Kodama, Masaaki Suzuki, and Yutaka Harano

Background: Nifedipine has been reported to cause impairment of insulin sensitivity. But recently a controlled-released formulation of nifedipine (nifedipine-GITS) has been reported that it could improve insulin sensitivity.

Methods: We evaluated insulin sensitivity in two groups of essential hypertensive subjects before and after treatment with either long-acting nifedipine (nifedipine-CR, Adalat CR tablets; Bayer Yakuhin, Osaka, Japan) \((n = 10)\) or metoprolol \((n = 9)\). Insulin sensitivity was evaluated from the steady-state plasma glucose (SSPG) level measured at the steady-state insulin level (20 to 30 \(\mu\)U/mL) using a modification of the SSPG method previously reported.

Results: The SSPG was initially high, but was significantly reduced by nifedipine-CR treatment (from 133 ± 14 mg/dL to 95 ± 8 mg/dL). However, SSPG was not significantly altered by treatment in the metoprolol group (from 103 ± 15 mg/dL to 119 ± 12 mg/dL).


Key Words: Calcium channel blockers, nifedipine, hypertension, insulin resistance, human.

Insulin resistance has been reported in essential hypertension, \(^1\) but whether this resistance is reversible by antihypertensive treatment remains to be determined. Treatment with vasodilating agents such as captopril \(^2\) and prazosin \(^3\) has been shown to improve insulin resistance. Most \(\beta\)-adrenoreceptor antagonists decrease insulin sensitivity, but those with a vasodilating effect can improve insulin sensitivity. \(^4\) Regarding the calcium-channel blockers, nifedipine treatment worsens glucose tolerance in patients with non-insulin-dependent diabetes \(^5\) and in nondiabetic subjects, \(^6,7\) and also deteriorates both insulin sensitivity and secretion. \(^8\) Conversely, diltiazem and verapamil were reported to have no effect on insulin sensitivity. \(^9\) We previously demonstrated an improvement of insulin sensitivity during treatment with amlodipine \(^10\) or benidipine, \(^11\) long-acting calcium channel blockers. Sheu et al \(^12\) showed that a controlled-released nifedipine (nifedipine-GITS) could improve insulin sensitivity. To clarify whether another long-acting nifedipine preparation (nifedipine-CR, Adalat CR tablets; Bayer Yakuhin, Osaka, Japan) could restore insulin sensitivity, we measured insulin sensitivity in hypertensive subjects without diabetes or obesity who were treated with either nifedipine-CR or a \(\beta\)-blocker, metoprolol. We also evaluated the changes of free fatty acids (FFAs) and ketone bodies during the insulin sensitivity test, as parameters of the action of insulin in liver or adipose tissue.

Methods

This investigation was carried out in 19 nonobese outpatients with hypertension and the results were compared with those obtained in seven healthy control subjects. The subjects had not been treated with any drugs for hypertension, and they had no other endocrine or metabolic disorders and no hepatic or renal dysfunction.

Using a mercury sphygmomanometer, systolic and diastolic blood pressures (BPs) were measured by detecting the Korotkoff phase I and V sounds, respectively. The mean of three BP measurements obtained on three different occasions with the subjects in the sitting position was calculated.

Hypertension was defined by a systolic BP exceeding 140 mm Hg or a diastolic BP that exceeded 90 mm Hg, whereas normotensive subjects were defined as having

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systolic and diastolic BP below 140 and 90 mm Hg, respectively.

The control subjects were all nondiabetic, nonobese, and normotensive individuals.

Hypertensive subjects were randomly assigned to treatment with either long-acting nifedipine (nifedipine-CR, 40 to 80 mg once a day, n = 10) or metoprolol (60 to 120 mg three times a day, n = 9) for 12 weeks. The target of treatment was to decrease the systolic BP below 140 mm Hg or the diastolic BP below 90 mm Hg. Patients were requested not to change their eating habits and daily activities during therapy.

Before and after treatment, the body weight was recorded and blood was collected for the measurement of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and apolipoprotein B (Apo B). A standard 75-g oral glucose tolerance test (OGTT) and an insulin sensitivity test were performed in all patients before and after treatment in the morning, after an overnight fast, before administration of drugs on that day. The area under the plasma concentration versus time curve (AUC) during OGTT was calculated for glucose and for insulin. Glucose tolerance was evaluated according to the criteria of the World Health Organization study group.13

**Insulin Sensitivity Test**

We modified the previously reported SSPG method using Sandostatin (octreotide acetate; Sandoz, Basel, Switzerland).14 Sandostatin was infused through an antecubital vein (125 μg as a bolus, followed by 100 μg/h) and Novolin R insulin (Novo Nordisk S/A, Tokyo, Japan, 7.5 mU/kg) was also given as a bolus followed by constant infusion at a rate of 0.385 μg/kg/min. Both drugs were infused for 2 h. A glucose solution (3 mg/kg/min) and KCl (0.25 μEq/kg/min) were also infused through an antecubital vein using an infusion pump. Blood samples were collected at 0, 30, and 120 min for the determination of glucose, insulin, TG, FFAs, and ketone bodies. Plasma epinephrine (E) and norepinephrine (NE) levels were also determined at 0 and 120 min. The plasma glucose level at 120 min (steady-state plasma glucose [SSPG]) was used as an indicator of insulin resistance. The infusion rates for glucose, KCl, and insulin were half of those previously reported,14 and the steady-state insulin level reached 20 to 40 mIU/mL. Under these conditions, the plasma glucose level was inversely correlated with insulin sensitivity and a higher SSPG value meant greater insulin resistance.

Plasma glucose was determined by the glucose oxidase method, and plasma insulin was measured by a two-antibody radioimmunoassay.15 The plasma concentrations of TC,16 TG,17 HDL-C,18apo B,19 ketone bodies,20 FFAs,21 E,22 and NE22 were determined as described elsewhere. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in square meters.

The fractional excretion of Na (FENa) during the insulin sensitivity test was calculated according to the following equation: FENa = Na clearance/creatinine clearance.

Informed consent was obtained from each subject.

**Statistical Analysis**

Results are presented as the mean ± standard error. Probability values <.05 (two-tailed) were defined as indicating statistical significance. The significance of differences among the control and hypertensive groups before treatment was determined by the Student t test. The male/female ratio was compared by the Fisher’s exact test. The paired t test was performed to compare the data of hypertensive subjects before and after treatment. Responses of various parameters during the insulin sensitivity test were analyzed using ANOVA and Student t test.

**Results**

**Baseline Characteristics**

The two hypertensive groups had significantly lower TG levels and higher HDL-C levels than the control group (Table 1). Comparing the nifedipine-CR and metoprolol groups, there were no significant differences in age, BMI, systolic BP, diastolic BP, heart rate, and the levels of TC, HDL-C, TG, glucose, insulin, and hemoglobin A1c. There were also no significant differences in AUC for glucose and insulin calculated from OGTT data.

After treatment, systolic and diastolic BP were significantly reduced in both the nifedipine-CR and metoprolol groups and the reductions were 35.7 ± 8.1/14.7 ± 4.7 mm Hg in the nifedipine-CR group and 16.9 ± 4.9/8.7 ± 1.8 in the metoprolol group. There was no significant difference between the two groups in the reduction of BP (systolic BP, P = .09; diastolic BP, P = .26).

Both treatments did not cause any significant changes of BMI, TC, TG, HDL-C, apo B, glucose, insulin, HbA1c, AUC of glucose, and AUC of insulin.

**Effects of Nifedipine-CR or Metoprolol on Insulin Sensitivity**

The SSPG level was initially elevated in both the nifedipine-CR group and the metoprolol group when compared with the control group (133 ± 14 mg/dL and 103 ± 15 mg/dL vs 82 ± 7 mg/dL), whereas there was no significant difference between the SSPG levels of the nifedipine-CR and metoprolol groups (Fig. 1). The SSPG level was significantly decreased by treatment with nifedipine-CR (95 ± 8 mg/dL), but did not change after metoprolol therapy (119 ± 12 mg/dL). All of the subjects in the nifedipine-CR group showed a decrease of SSPG, indicating an improvement of insulin sensitivity. In contrast, the steady-state plasma insulin levels were not changed by treatment in both groups.
Table 1. Baseline characteristics of each group

<table>
<thead>
<tr>
<th></th>
<th>Nifedipine-CR</th>
<th>Metoprolol</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Age (y)</td>
<td>61.8 ± 4.4</td>
<td>63 ± 5</td>
<td>60.3 ± 2.2</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>3/7</td>
<td>3/6</td>
<td>3/4</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.4 ± 0.5</td>
<td>22.2 ± 0.4</td>
<td>22.8 ± 1.8</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>168.3 ± 7.2*</td>
<td>132.6 ± 4.1§</td>
<td>147.5 ± 4.6*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>96.2 ± 4.8*</td>
<td>81.5 ± 3.5§</td>
<td>83.9 ± 4.9*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>70.1 ± 3.8</td>
<td>70.9 ± 3.5</td>
<td>73.3 ± 8.8</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>201.2 ± 8.6</td>
<td>193.3 ± 7.3</td>
<td>186.6 ± 16.4</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>59.3 ± 3.9*</td>
<td>61 ± 6.2</td>
<td>56 ± 8.7*</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>87 ± 8.8†</td>
<td>78 ± 9.9</td>
<td>88.5 ± 21†</td>
</tr>
<tr>
<td>Free fatty acids (U/mL)</td>
<td>495.3 ± 43.1</td>
<td>462.3 ± 57.4</td>
<td>576.6 ± 135.8</td>
</tr>
<tr>
<td>Apoprotein B (mg/dL)</td>
<td>87.2 ± 6.5</td>
<td>76 ± 12</td>
<td>82.9 ± 10.4</td>
</tr>
<tr>
<td>Plasma insulin (U/mL)</td>
<td>7.8 ± 3</td>
<td>4.5 ± 0.5</td>
<td>6.2 ± 1</td>
</tr>
<tr>
<td>Plasma glucose (mg/dL)</td>
<td>89.8 ± 2.5</td>
<td>92.2 ± 2.9</td>
<td>73.8 ± 18.2</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.5 ± 0.3</td>
<td>5.3 ± 0.2</td>
<td>4.7 ± 0.1</td>
</tr>
<tr>
<td>AUC of glucose (mg/dL · h)</td>
<td>267.1 ± 20.8</td>
<td>274 ± 17.8</td>
<td>307.7 ± 15.7</td>
</tr>
<tr>
<td>AUC of insulin (U/mL · h)</td>
<td>83.9 ± 11.4</td>
<td>87.2 ± 17.6</td>
<td>79.8 ± 24.8</td>
</tr>
<tr>
<td>HOMA-R</td>
<td>1.87 ± 0.82*</td>
<td>0.99 ± 0.15</td>
<td>1.23 ± 0.19*</td>
</tr>
</tbody>
</table>

HDL = high-density lipoprotein; HbA1c = hemoglobin A1c; area under curve (AUC) of glucose or insulin area under the plasma glucose or plasma insulin versus time curve in the OGTT; HOMA-R = homeostasis model assessment for insulin resistance index; OGTT = oral glucose tolerance test.

Values are the mean ± SE.

* P < .05; † P < .01 for before nifedipine-CR or metoprolol treatment versus control by the t test; ‡ P < .05; § P < .01 for before versus after nifedipine-CR or metoprolol treatment by the t test.

Changes of Serum FFAs and Ketone Bodies During the Insulin Sensitivity Test

Serum FFAs and ketone bodies showed a significant decrease at 30 min during the insulin sensitivity test both before and after treatments in all groups (Fig. 2). There was a significant difference in the FFAs response before and after nifedipine-CR treatment (P < .05, ANOVA), with the reduction of FFAs at 30 min being significantly greater after treatment than before treatment (P < .05, t test). The reduction of ketone bodies was also greater after nifedipine-CR treatment than before treatment, but the difference did not reach statistical significance (P = .13).

Changes of E, NE, and FENa During the Insulin Sensitivity Test

There were no significant changes of circulating E and NE levels or FENa after treatment with either drug (Table 2). There were no significant changes of E, NE, and FENa values during insulin sensitivity testing in the control or hypertensive subjects before and after treatment.

Discussion

Administration of long-acting nifedipine (nifedipine-CR) for 12 weeks to subjects with hypertension was able to decrease the SSPG value. The observed paired decrease of SSPG in the 10 hypertensive subjects is highly significant from our experience in a large number of subjects (> 500). This improvement of insulin sensitivity after nifedipine-CR treatment is valid even in the nonstatistical variation of basal SSPG and BP levels between the two groups with these treatments and those with metoprolol. In contrast to the previous observation,5 the metoprolol treatment has not further reduced insulin sensitivity with the regular dose of administration. The clinical usefulness of β-blockers in subjects with cardiovascular disease has been well established and our data support this concept from the standpoint of insulin sensitivity. Steady-state plasma insulin has been quite stable and no significant difference has been observed in the two treatment groups before and after the treatment. The half dose of insulin and glucose compared with the SSPG method previously reported is used in the present study to diminish the fluid volume of influ-
Although the data are not shown, continued infusion with arginine has been attempted.

The reduction of FFAs at 30 min during insulin sensitivity testing was greater after nifedipine-CR treatment, indicating the improvement of insulin sensitivity for antilipolytic action.

Homeostasis model assessment-insulin resistance index tended to decrease in the nifedipine-CR group but the change was not significant. The AUC of glucose and insulin did not change. Improvement of insulin sensitivity by nifedipine-CR may not have been large enough to influence the insulin and glucose levels during OGTT.

We have reported an improvement in insulin sensitivity after treatment with amlodipine 10 and benidipine, 11 which belong to the same class of dihydropyridine derivatives as nifedipine. Amlodipine associates and dissociates more slowly from the calcium channel than nifedipine, 23 whereas benidipine binds to cell membrane binding sites from which it dissociates slowly, 24 and both drugs are longer acting than nifedipine.

Sheu et al 12 reported that a controlled-released type nifedipine (nifedipine-GITS) could improve insulin sensitivity. Nifedipine-CR is a newly developed sustained-release for once-a-day administration, which consists of a rapidly dissolving core surrounded by a slowly dissolving coat.

Calcium channel blockers may inhibit insulin secretion in vitro. 8 There was no change of the AUC for insulin in the OGTT results before and after nifedipine-CR treatment, indicating that insulin secretion was not impaired in the present study.

In this study, there was no elevation of catecholamine levels or heart rate change during the insulin sensitivity test. The insulin-induced activation of the sympathetic nervous system was not observed in the present study.

An increased intracellular calcium level seems to be associated with insulin resistance in essential hypertension. We have previously reported that the platelet free calcium concentration was positively correlated with the SSPG level in hypertension. 11 Elevated intracellular cal-

**Table 2.** Changes of epinephrine, norepinephrine, and fractional Na excretion during the insulin sensitivity test after nifedipine-CR or metoprolol treatment

<table>
<thead>
<tr>
<th></th>
<th>Nifedipine-CR</th>
<th></th>
<th>Metoprolol</th>
<th></th>
<th>Control</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Min</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Epinephrine (pmol/L)</td>
<td>0 26.4 ± 6.8</td>
<td>30.1 ± 6.8</td>
<td></td>
<td>48.5 ± 20.1</td>
<td>53.5 ± 10.7</td>
</tr>
<tr>
<td></td>
<td>120 23.3 ± 4.8</td>
<td>28.9 ± 10.2</td>
<td></td>
<td>19.4 ± 5.6</td>
<td>25.5 ± 4.9</td>
</tr>
<tr>
<td>Norepinephrine (pmol/L)</td>
<td>0 463.8 ± 132.7</td>
<td>371.9 ± 70.3</td>
<td></td>
<td>757.3 ± 405.9</td>
<td>830.8 ± 25</td>
</tr>
<tr>
<td></td>
<td>120 433.7 ± 106.6</td>
<td>373.3 ± 79.1</td>
<td></td>
<td>492.4 ± 192.8</td>
<td>411.5 ± 185.8</td>
</tr>
<tr>
<td>Fractional excretion of Na</td>
<td>0 0.6 ± 0.1</td>
<td>0.6 ± 0.2</td>
<td></td>
<td>0.5 ± 0.2</td>
<td>0.7 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>120 0.8 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td></td>
<td>1.4 ± 0.7</td>
<td>1.0 ± 0.2</td>
</tr>
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</table>

**FIG. 2.** Changes of serum free fatty acids and ketone bodies in the insulin sensitivity test before and after nifedipine-CR or metoprolol treatment. Black circles = before treatment; white circles = after treatment. Values are the mean ± SE. P value or NS for the response before versus after treatment by ANOVA. The bar graphs (black columns = before treatment; white columns = after treatment) shows the reduction of free fatty acids or ketone bodies at 30 min during the insulin sensitivity test. P value for before versus after treatment by the t test. Other abbreviation as in Fig. 1.
Hypertension.

metabolism as indicated by decreased SSPG, whereas nifedipine-CR improved insulin sensitivity for glucose hypertensive subjects before or after treatment at physiologic levels. However, we found no changes of TC, TG, HDL-C, or Apo B after nifedipine-CR treatment.

Increased renal sodium reabsorption was reported un-


References


