Effect of Indapamid SR in the Treatment of Hypertensive Patients With Type 2 Diabetes

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Background: To evaluate the effect of the sustained-release formulation of indapamide (indapamide SR) in type 2 diabetic patients with mild-to-moderate hypertension and its possible side effects, particularly on glucose metabolism and lipid profiles.

Methods: A total of 64 patients randomly received 1.5 mg of indapamide SR or placebo once daily for 3 months. The effects were evaluated by 24-h ambulatory blood pressure monitor, fasting blood sampling for biochemistry, lipid profiles, and frequently sampled intravenous glucose tolerance test.

Results: The changes in standing and supine blood pressure (BP) were significant (154.7 ± 9.494 ± 2.9 mm Hg v 134.4 ± 5.1/82.4 ± 5 mm Hg and 155 ± 9.8/94.6 ± 3.6 mm Hg v 135.1 ± 4.9/82.1 ± 4.7 mm Hg) in the indapamide group, but not in the placebo group. According to the 24-h ambulatory blood pressure monitor reading, a significant reduction was observed in not only in the whole-day mean BP (mean systolic BP/mean diastolic BP, 149 ± 19.3/87.6 ± 11.3 mm Hg v 135.7 ± 12.6/79.6 ± 9 mm Hg) but also the whole-day mean median arterial pressure (109 ± 12.7 mm Hg v 98.7 ± 8.2 mm Hg) for the indapamide group, but not the placebo group. There were no changes in biochemical data including serum sodium, potassium, chloride, uric acid, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, lipid profiles, fasting blood glucose, insulin, hemoglobin A1c, and glucose metabolism parameters (insulin sensitivity, glucose effectiveness, and acute insulin response) from frequently sampled intravenous glucose tolerance test after indapamide or placebo therapy.

Conclusions: Indapamide SR can significantly lower the whole-day BP in hypertensive patients with type 2 diabetes. Also, it did not alter or aggravate patients’ lipid profiles, glucose metabolism, and did not exert possible side effects of hypokalemia and hyperuricemia. Therefore, monotherapy with indapamide SR should be suggested in type 2 diabetic patients with mild-to-moderate hypertension. Am J Hypertens 2003;16:623–628 © 2003 American Journal of Hypertension, Ltd.

Key Words: Indapamide SR, hypertension, diabetes mellitus.
moderate hypertension and to verify the efficacy and its possible side effects, particularly on glucose metabolism and lipid profile.

Methods
Study Patients
Sixty-four ambulatory patients with a diagnosis of type 2 diabetes mellitus according to the specifications of the National Diabetes Data Group, who were being treated with oral hypoglycemic agents (sulfonylurea/metformin) or diet control alone formed the study group. They also had arterial hypertension of mild-to-moderate degree demonstrated by supine diastolic blood pressure (DBP) between 90 and 115 mm Hg, and systolic blood pressure (SBP) between 140 and 180 mm Hg. They were treated with a single antihypertensive agent. All subjects gave their written informed consent after explanation of the study by the investigator and the Local Ethics Committee approved the study.

Patients presenting with at least one of the following criteria were not included: 1) severe hypertension: supine DBP >115 mm Hg or supine SBP >210 mm Hg at any time during the washout period; 2) symptomatic or treated coronary heart disease, congestive heart failure; 3) significant renal, hepatic, or neurologic disease; 4) obesity, body mass index ≥30; 5) gouty arthritis within the previous 3 months; and 6) hypokalemia with serum potassium <3.5 mmol/L.

Experimental Design
Selected patients had to discontinue any antihypertensive treatment and be included into a 2-week washout period to confirm the stability of the hypertension. The oral hypoglycemic agent remained unchanged during the study period. If mild-to-moderate hypertension is confirmed after the washout period and any of the exclusion criteria were absent, patients randomly received one 1.5-mg indapamide SR tablet or placebo per day at breakfast for 12 weeks. It was administered after BP measurement on each visit. After a 30-min rest in the sitting position, three BP and pulse rate (PR) readings were obtained at 5-min intervals. The BP were recorded by the same person with a standard sphygmomanometer according to the directives of the American Heart Association. The average of the three readings was taken as the BP and PR for that particular visit. The efficacy of treatment was evaluated monthly in terms of changes in baseline values in both supine and standing SBP and DBP.

Ambulatory BP Monitoring and Trough-to-Peak Ratio
In addition to conventional sphygmomanometry, all patients underwent 24-h ambulatory BP monitoring (ABPM) on the last day of the washout period and the last day of the treatment period (W12). The device was an Oscar oscillometric ABPM (Sun Tech Medical Instruments, England). All patients were fitted with the device between 8 and 10 AM, 24 h after the last dose, during a day of normal activity. Dosing was performed after fitting; the device was removed by the investigator 24 h later, the following morning, before the next dose. The device was programmed to record BP every 15 min from 6 AM to 10 PM and every 30 min from 10 PM to 6 AM.

Since 1988, the Food and Drug Administration has recommended a new arithmetic index, the trough-to-peak ratio, for monitoring antihypertensive drug activity (recommended minimal value of 50%). The trough-to-peak ratio describes the relationship between the antihypertensive effect at the end of the dosing interval (trough) and maximal effect (peak) by simple arithmetic division, expressed as a percentage.

Laboratory Measurements
Blood samples were obtained in the morning before eating and drug intake at W0 and W12 for analysis of fasting blood glucose, insulin, glycosylated hemoglobin (HbAlc), blood urea nitrogen (BUN), creatinine (Cr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), uric acid (UA), total cholesterol (TC), triglyceride (TG), HDL-cholesterol, and electrolytes (Na, K, Cl, Ca). Serum concentrations of BUN, Cr, AST, ALT, UA, TC, TG, and electrolytes were measured using a dry multilayer analytic slide method in the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film Corporation, Minato-Ku, Tokyo, Japan). Serum HDL-cholesterol levels were determined with an enzymatic cholesterol assay method after dextran sulfate precipitation. The plasma glucose concentration was determined by the glucose oxidase method on a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Plasma insulin was measured with a commercial radioimmunoassay kit (Coat-A-Count Insulin Kit, Diagnostic Products Corporation, Los Angeles, CA). The intra-assay and interassay coefficients of variance for insulin are 3.3% and 2.5%, respectively. The HbAlc was measured by Bio-Rad Variant II automatic analyzer (Bio-Rad Diagnostic Group, Los Angeles, CA).

Frequently Sampled Intravenous Glucose Tolerance Test
Between 7 to 9 AM, after a 12-h fast, an indwelling cannula was inserted into an antecubital vein for injection of glucose and insulin. Another cannula for blood sampling was inserted into the antecubital vein of the opposite arm. An insulin-modified frequently sampled intravenous glucose tolerance test (FSIGT) with 21 blood samples was performed to evaluate insulin sensitivity. Fasting blood
samples for the measurement of plasma-specific insulin and two successive blood samples (5 min apart) for the measurement of fasting blood glucose and plasma immunoreactive insulin (IRI) levels were taken. An intravenous glucose bolus (0.3 g glucose/kg body weight as 50% solution administered during 90 sec) was then injected through the cannula in the arm opposite to the sampling arm.

Additional samples for blood glucose and plasma IRI levels were taken at 1, 2, 3, 4, 5, 6, 8, 10, 14, 19, 22, 25, 30, 40, 50, 70, 100, 140, and 180 min. At 20 min, an intravenous injection of regular insulin (0.05 U/kg body weight) was administered to increase the accuracy of the modeling analyses. Glucose utilization was analyzed with the minimal model of glucose disappearance of Bergman et al.16 and Welch et al.17 The minimal model provides a measure of the sensitivity of glucose elimination to insulin (S_i; inversely proportional to insulin resistance). Estimates of S_i from this model have been validated against the glucose clamp technique. Acute insulin response (AIR) is the increment in the plasma IRI concentration above baseline in the first 10 min (measured at 4, 6, 8, and 10 min) after glucose administration. E_G is the effect of glucose, independent of insulin, on the glucose utilization rate, also obtained by using a minimal model algorithm. The Bergman minimal model attempts to directly estimate insulin sensitivity (insulin-dependent glucose uptake), but its utilization in diabetics is still controversial.18,19

### Adverse Events

Patients were interviewed at each visit to elicit any spontaneously reported adverse events (including intercurrent illness or accidents). These events were described in detail (date of onset, description of symptoms, duration, severity, outcome, ie, whether any additional treatment is required, and follow up). In addition, the investigator indicated whether in his opinion the adverse event is therapy related. If adverse drug reactions occurred, indapamide SR had to be discontinued immediately and patients would be withdrawn from this study.

### Table 1. Changes in standing and supine blood pressure and heart rate before and after indapamide SR 1.5 mg or placebo treatment

<table>
<thead>
<tr>
<th></th>
<th>Standing</th>
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<tr>
<td></td>
<td>SBP (mm Hg)</td>
<td>DBP (mm Hg)</td>
<td>HR (beats/min)</td>
<td>SBP (mm Hg)</td>
<td>DBP (mm Hg)</td>
<td>HR (beats/min)</td>
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<tr>
<td>Indapamide group</td>
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<tr>
<td>Before</td>
<td>154.7 ± 9.4</td>
<td>94 ± 2.9</td>
<td>80 ± 6.7</td>
<td>154.9 ± 9.8</td>
<td>94.6 ± 3.6</td>
<td>80 ± 7.1</td>
</tr>
<tr>
<td>After</td>
<td>134.4 ± 5.1*</td>
<td>82 ± 4*</td>
<td>79 ± 7.2</td>
<td>135.1 ± 4.9*</td>
<td>82.1 ± 4.7*</td>
<td>79 ± 6.6</td>
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<tr>
<td>Placebo group</td>
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<tr>
<td>Before</td>
<td>152.6 ± 7.8</td>
<td>92 ± 3.5</td>
<td>78 ± 5.1</td>
<td>153.7 ± 8.1</td>
<td>93 ± 4.1</td>
<td>80 ± 5.2</td>
</tr>
<tr>
<td>After</td>
<td>150.8 ± 9.1</td>
<td>90 ± 6.1</td>
<td>76 ± 4.2</td>
<td>150.2 ± 5.1</td>
<td>91 ± 5.2</td>
<td>79 ± 6.0</td>
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</table>

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.

Data are expressed as mean ± SD.

* P < .001 compared between before and after indapamide treatment.

### Statistical Analysis

All of the data was expressed as mean ± standard deviation, statistical significance between before and after treatment groups are compared using a paired t test. A P value of < .05 was considered significant.

### Results

#### General Data

Sixty-four type 2 diabetic patients (men/women = 30/34) were enrolled into this study with a mean age of 59.8 ± 8.7 years. Finally, 60 patients completed this study and four were withdrawn. The causes of withdrawal were adverse events (one patient had a head injury and one patient had a heart attack), noncompliance (one patient), and insufficient therapeutic effect (one patient).

#### Effects of Indapamide SR on Arterial BP

The changes in standing BP were significant not only for SBP (154.7 ± 9.4 mm Hg v 134.4 ± 5.1 mm Hg, P < .001), but also DBP (94 ± 2.9 mm Hg v 82 ± 4 mm Hg, P < .001) in the indapamide group, but not in the placebo group. The same reductions in supine BP were noted in SBP (154.9 ± 9.8 mm Hg v 135.1 ± 4.9 mm Hg, P < .001) and DBP (94.6 ± 3.6 mm Hg v 82.1 ± 4.7 mm Hg, P < .001) (Table 1). But no change was found in both the standing and supine heart rate. According to the 24-h ABPM reading, a significant reduction was observed in the whole-day mean BP (mean SBP/mean DBP) (148.9 ± 19.3 mm Hg v 135.7 ± 12.6 mm Hg and 87.6 ± 11.3 mm Hg v 79.6 ± 8.9 mm Hg, P < .001, respectively), and the whole-day mean median arterial pressure (mean MAP) (109 ± 12.7 mm Hg v 98.7 ± 8.2 mm Hg, P < .001) in the indapamide group, but not in the placebo group (Table 2). In addition, a similarly significant reduction in mean SBP, mean DBP, and mean MAP was also shown in daytime and nighttime in the indapamide group (Table 2). The trough-to-peak ratios of SBP (0.55), DBP (0.51), and MAP (0.61) were better than 0.5.
Effect of Indapamide on the Glucose Metabolism

No significant changes of fasting blood glucose, insulin, and HbAlc levels were found in both groups (Table 3). For glucose metabolism, no marked changes from frequently sampled intravenous GTT data (S_I, E_G, and AIR) were found in both groups (Table 3).

Effect of Indapamide on Biochemical Data

There were no changes in biochemical data including serum potassium, uric acid, ALT, AST, BUN, Cr, and lipid profiles (total cholesterol, triglyceride, HDL-cholesterol) before and after both treatment.

Discussion

It is widely known that antihypertensive treatment in patients with diabetes mellitus should be carried out with caution. After the first report on an antihypertensive effect of thiazide diuretics, it was soon pointed out that diuretics may have a diabetogenic action and may unmask a diabetic condition or aggravate preexisting diabetes, particularly in the elderly in whom progressive deterioration of the carbohydrate metabolism occurs. The mechanism by which glucose tolerance is impaired with thiazide is only partly elucidated, but has been demonstrated to be linked to hypokalemia, resulting in insulinopenia, diminished β-cell responsiveness to the glucose stimulus, or impaired conversion of proinsulin. Indapamide does not appear to have the same effect on the serum

Table 2. Changes in 24-hour ABPM of whole day before and after indapamide SR 1.5 mg or placebo treatment

<table>
<thead>
<tr>
<th></th>
<th>Indapamide Group</th>
<th>Placebo Group</th>
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<tr>
<td></td>
<td>Before</td>
<td>After</td>
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<tr>
<td>Whole day ABPM</td>
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<tr>
<td>mSBP (mm Hg)</td>
<td>148.9 ± 19.3</td>
<td>135.7 ± 12.6*</td>
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<tr>
<td>mDBP (mm Hg)</td>
<td>87.6 ± 11.3</td>
<td>79.6 ± 8.9*</td>
</tr>
<tr>
<td>mMAP (mm Hg)</td>
<td>109 ± 12.7</td>
<td>98.7 ± 8.2*</td>
</tr>
<tr>
<td>Daytime ABPM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mSBP (mm Hg)</td>
<td>149 ± 19.6</td>
<td>135.7 ± 11.7*</td>
</tr>
<tr>
<td>mDBP (mm Hg)</td>
<td>88.1 ± 11.4</td>
<td>79.9 ± 9.6*</td>
</tr>
<tr>
<td>mMAP (mm Hg)</td>
<td>109.4 ± 13</td>
<td>98.9 ± 8.2*</td>
</tr>
<tr>
<td>Nighttime ABPM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mSBP (mm Hg)</td>
<td>147.1 ± 18.2</td>
<td>135.4 ± 14.5*</td>
</tr>
<tr>
<td>mDBP (mm Hg)</td>
<td>87.2 ± 11.5</td>
<td>79.2 ± 9.4*</td>
</tr>
<tr>
<td>mMAP (mm Hg)</td>
<td>107.62 ± 12.3</td>
<td>98.2 ± 9.4*</td>
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mSBP = mean systolic blood pressure; mDBP = mean diastolic blood pressure; ABPM = ambulatory blood pressure monitoring; mMAP = mean median arterial pressure.

* P < .001 compared between before and after indapamide treatment.

Table 3. Changes in plasma glucose and insulin levels and results from FSIGT before and after indapamide SR 1.5 mg or placebo treatment

<table>
<thead>
<tr>
<th></th>
<th>Indapamide Group</th>
<th>Placebo Group</th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>189.4 ± 87.2</td>
<td>203.6 ± 77.2</td>
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<tr>
<td>Fasting plasma insulin (μU/mL)</td>
<td>27.5 ± 11.3</td>
<td>31.2 ± 21.2</td>
</tr>
<tr>
<td>HbAlc (%)</td>
<td>8.3 ± 2.5</td>
<td>8.4 ± 1.9</td>
</tr>
<tr>
<td>Insulin sensitivity (S_I, 10^{-5}min^{-1}/pM)</td>
<td>1.37 ± 0.88</td>
<td>1.18 ± 1.21</td>
</tr>
<tr>
<td>Glucose effectiveness (E_G, min^{-1})</td>
<td>0.023 ± 0.011</td>
<td>0.021 ± 0.012</td>
</tr>
<tr>
<td>Acute insulin response (AIR, pM)</td>
<td>4621 ± 786.1</td>
<td>4290 ± 879.7</td>
</tr>
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</table>

FSIGT = frequently sampled intravenous glucose tolerance test; SR = sustained-release formulation of indapamide; HbA1c = glycosylated hemoglobin.

Discussion

It is widely known that antihypertensive treatment in patients with diabetes mellitus should be carried out with caution. After the first report on an antihypertensive effect of thiazide diuretics, it was soon pointed out that diuretics may have a diabetogenic action and may unmask a diabetic condition or aggravate preexisting diabetes, particularly in the elderly in whom progressive deterioration of the carbohydrate metabolism occurs. The mechanism by which glucose tolerance is impaired with thiazide is only partly elucidated, but has been demonstrated to be linked to hypokalemia, resulting in insulinopenia, diminished β-cell responsiveness to the glucose stimulus, or impaired conversion of proinsulin. Indapamide does not appear to have the same effect on the serum glucose metabolism. However, careful monitoring and appropriate adjustments in the antihypertensive regimen are necessary to minimize this potential adverse effect.
potassium level as thiazides, which may explain the failure of the drug to adversely affect glucose tolerance.

After reviewing all of the previous reports, our study is the first to use a more scientific method to evaluate the effect of indapamide on glucose metabolism (insulin sensitivity and β-cell function). No significant modifications of fasting glycemia, postprandial glycemia, and glycosylated hemoglobin were observed previously after 2.5 mg of indapamide daily therapy. This study further confirmed that 1.5 mg of indapamide SR is not only an effective antihypertensive agent, but causes no deterioration in glucose tolerance and glycemic control in hypertensive type 2 diabetic patients. The good tolerance for indapamide should also be noted for the other biochemical parameters (total cholesterol, triglyceride, and HDL-cholesterol levels), which are often disturbed in type 2 diabetes.

No significant changes in serum sodium, potassium, chloride, calcium, and uric acid levels were observed in our patients. Many previous works showed that hypokalemia is absent or minimal during treatment with 2.5 mg/day of indapamide. The minimal action of indapamide is absent or minimal during treatment with 2.5 mg/day of indapamide. Many previous works showed that hypokalemia is absent or minimal during treatment with 2.5 mg/day of indapamide. The minimal action of indapamide is absent or minimal during treatment with 2.5 mg/day of indapamide. Many previous works showed that hypokalemia is absent or minimal during treatment with 2.5 mg/day of indapamide. The minimal action of indapamide is absent or minimal during treatment with 2.5 mg/day of indapamide. Many previous works showed that hypokalemia is absent or minimal during treatment with 2.5 mg/day of indapamide. The minimal action of indapamide is absent or minimal during treatment with 2.5 mg/day of indapamide.

The sustained BP reduction obtained in our study was similar to those achieved with other antihypertensive therapies and previous reports using indapamide. However, unlike the thiazide diuretics and some β-blockers, indapamide did not significantly alter the serum total cholesterol, triglyceride, and HDL-cholesterol levels. This is in agreement with several previous reports. Indapamide has a diuretic effect; it is also a known potent vasodilator by both adrenergic blocking and a probable calcium antagonistic mechanism, as demonstrated experimentally in animals. These effects may be linked to the favorable lipoprotein changes reported previously. These advantages have been convincingly shown to be associated with a lower risk of coronary heart disease in most epidemiologic and intervention studies. In addition, 24-h ABPM showed that the standard dosage of 1.5 mg of indapamide SR once daily provided sustained BP control during 24 h, thus facilitating good patient compliance.

Steady-state plasma levels are reached within 3 to 4 days after starting indapamide SR treatment, and the drug does not accumulate in patients with various degrees of renal insufficiency. Many studies showed that indapamide can reduce BP and albumin excretion rates without affecting the glomerular filtration rate in both normotensive and hypertensive patients with microalbuminuria.

In summary, 1.5 mg of indapamide SR is an effective and safe antihypertensive agent for patients with mild-to-moderate hypertension and type 2 diabetes. Its advantages including sustained reduction of BP, attenuated lipid, glucose, and potassium side effects, and cost effectiveness all render 1.5 mg of indapamide SR an effective antihypertensive agent for the treatment of hypertension in type 2 diabetic patients.

Acknowledgments

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References