Indapamide in the Treatment of Hypertension in Non-Insulin-Dependent Diabetes

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SUMMARY The antihypertensive effect of indapamide, a new thiazide derivative, has a low diuretic effect and a primary action on vascular smooth muscle. It was evaluated in a series of 20 patients with non-insulin-dependent diabetes (age range 47-75 years) who had arterial hypertension of mild to moderate degree treated with hypoglycemic agents and/or diet. Indapamide, 2.5 mg, was given as a single daily dose for 6 months. A statistically significant reduction of systolic and diastolic pressures was observed in both supine and upright positions. This decrease was significant beginning in the first month of therapy ($p < 0.001$). No significant modifications of fasting glycemia, postprandial glycemia, and glycosylated hemoglobin were noted. No significant changes were observed in serum sodium, potassium, chloride, calcium, and uric acid. Indapamide is an effective and practical treatment of hypertension of mild to moderate degree in patients with diabetes. The absence of effect on glucose metabolism makes it an especially interesting drug. (Hypertension 7 [Supp II]: II-157-11-160, 1985)

KEY WORDS • blood pressure • diabetes mellitus

Moreover, insulin secretion may be decreased by thiazide-induced hypokalemia per se, with a defect in beta cell responsiveness to glucose stimulus. It is interesting that hypokalemia appears to interfere with the conversion of proinsulin to insulin in the beta cell, so that larger amounts of the less active proinsulin are released in the blood. Correction of thiazide-induced hypokalemia has been shown to improve glucose tolerance.

The use of beta blockers in hypertensive diabetic patients also poses problems because it seems possible that they may mask an hypoglycemic reaction or prolong the recovery phase from a hypoglycemic episode through suppression of the response of the counterregulatory hormones. Attempts to avoid these untoward effects by using selective beta, blockers such as acebutolol or atenolol have been inconclusive, and it has been reported that metoprolol does not change glucose tolerance in hypertensive diabetic patients.

The search for a better diuretic with milder side effects led to the synthesis of indapamide, a derivative of thiazide-type diuretics in which the introduction of a methyl indoline substituent makes the molecule highly lipophilic, with greater affinity for vascular smooth muscle and a direct prevailing vasodilating effect with respect to the retained diuretic action. The vascular action of indapamide has been clearly documented as inhibition of the vascular response to norepinephrine,
epinephrine, and angiotensin II. A decrease in vascular reactivity has been also demonstrated in vivo in experimental animals and in humans. The reduction in vascular reactivity may be due to inhibition of transmembrane calcium influx.

We evaluated the effects of indapamide in a series of patients with non-insulin-dependent diabetes and mild to moderate hypertension to verify the efficacy of indapamide and its possible side effects, particularly on glucose metabolism.

Materials and Methods

The 20 ambulatory patients studied (8 men, 12 women; mean age 55.85 ± 7.54 [SD], range 47–75 years) had a diagnosis of non-insulin-dependent diabetes according to specifications of the National Diabetes Data Group. They were being treated with glibenclamide (5–15 mg/day) or diet alone. They also had arterial hypertension of mild to moderate degree demonstrated by supine diastolic arterial pressure between 95 and 115 mm Hg. None was markedly obese and none had significant renal, hepatic, or neurological diseases.

After a 15-day washout period of all hypotensive drugs given previously, the patients received indapamide, 2.5 mg per day, in a single dose in the morning for 24 weeks. Blood pressure was measured by a standard mercury sphygmomanometer according to the directive of the American Heart Association. The averages of three supine and three subsequent standing blood pressure readings were recorded. The efficacy of treatment was evaluated monthly in terms of changes in baseline values in both supine and standing systolic and diastolic pressures. Before, during, and after the study period, basal glycemia, 2-hour postprandial glycemia, glycosylated hemoglobin, serum sodium, potassium, chloride, calcium, and uric acid were evaluated. Stable glycosylated hemoglobin was evaluated by a microcolumn method as fast hemoglobins measuring HbAIA+B+c (Boehringer, Mannheim, West Germany). Removal of labile glycosylated hemoglobin was obtained by incubating red blood cells for 6 hours at 37 °C in 0.9% saline solution prior to chromatography. The intraassay and interassay coefficients of variation were 5.8 and 9.8% respectively. Statistical analysis was performed by the paired t test.

Results

Indapamide 2.5 mg daily for 24 weeks induced a stable reduction of both systolic and diastolic blood pressure values in supine and standing positions in non-insulin-dependent diabetic patients (Figure 1). The antihypertensive effect of indapamide was prompt and statistically significant (p < 0.001) after the first month of therapy and persisted for the entire treatment period. Fasting glycemia, 2-hour postprandial glycemia, and glycosylated hemoglobin were not significantly affected during treatment (Figures 2 and 3). Baseline and 6-month values (± SEM) for fasting glycemia (FG), postprandial glycemia (PG), and glycosylated hemoglobin (HbA1c) were as follows: FG, 152.33 ± 15.84 and 152.73 ± 9.08 mg/dl, NS; PG, 191.50 ± 19.66 and 202.27 ± 19.22 mg/dl, NS; HbA1c, 9.34 ± 0.63 and 8.80 ± 0.49%, NS. Levels of serum sodium, potassium, chloride, calcium, and uric acid were not statistically modified by indapamide (Table 1). The moderate increase of serum uric acid concentration, statistically not significant, did not exceed the values of the upper limit of normal range. No variations of mean body weight were recorded (Table 1). No patient required potassium supplements. No unusual or unexpected adverse reactions were noted except a transient headache and nausea in two patients. No patient discontinued treatment because of adverse reaction or abnormal laboratory values.
No significant modifications of serum sodium, potassium, chloride, calcium, and uric acid were observed in our patients. Many previous works showed that hypokalemia is absent or minimal during treatment with 2.5 mg/day of indapamide.26-28 A dose-dependent increase in natriuresis and kaliuresis was demonstrated by Caruso et al.,29 and occurred also with 2.5 mg/day. The minimal action of indapamide on serum potassium is particularly beneficial in hypertensive diabetic patients in whom hypokalemia may suppress insulin release6 with subsequent carbohydrate intolerance.

In summary, within the limits of an open study, it seems from our results that indapamide is an effective and safe treatment for hypertension in patients with non-insulin-dependent diabetes, and causes no significant alterations on glucose metabolism. Before definite conclusions can be drawn, however, further controlled studies are necessary to verify the safety of the drug for longer periods of time with respect to glucose control.

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 action22'23 and may unmask a diabetic condition or aggravate preexisting diabetes, particularly in the elderly in whom progressive deterioration of carbohydrate metabolism occurs.24

In our study we evaluated the effect of indapamide, a new thiazide derivative in which the introduction of a methyl-indole substituent gives the drug highly lipophilic properties with a direct vascular effect. While at a dose of 5 mg/day and above indapamide retains major diuretic properties, the 2.5-mg/day dose may have a modest diuretic effect and a prevailing vasodilating action, possibly with fewer side effects than the classic thiazide diuretics. In our series of patients with non-insulin-dependent diabetes, prompt and stable reduction of systolic and diastolic pressures was obtained without deterioration of glucose metabolism.

No significant modifications of fasting glycemia, postprandial glycemia, and glycosylated hemoglobin were observed. Our results confirm those of Roux et al.,25 who were not able to demonstrate any deterioration of glucose control in a series of insulin- and non-insulin-dependent diabetic persons treated with indapamide, 2.5 mg daily.

| TABLE 1. Laboratory Values Before and During Treatment with Indapamide 2.5 mg/day (mean ± SEM) |
|---------------------------------|------------------|------------------|------------------|------------------|
|                                | Baseline         | 8th week         | 16th week        | 24th week        |
| Sodium (mEq/L)                 | 138.58 ± 0.62    | 137.67 ± 0.81**  | 138.00 ± 0.69*   | 139.55 ± 0.55*   |
| Potassium (mEq/L)              | 4.05 ± 0.09      | 4.14 ± 0.12*     | 4.23 ± 0.15*     | 4.32 ± 0.16*     |
| Chloride (mEq/L)               | 98.42 ± 0.71     | 98.83 ± 0.58*    | 100.64 ± 0.98*   | 98.64 ± 0.69*    |
| Calcium (mg/100 ml)            | 9.49 ± 0.12      | 9.59 ± 0.14*     | 9.71 ± 0.14*     | 9.71 ± 0.14*     |
| Urine (mg/100 ml)              | 4.60 ± 0.61      | 5.06 ± 0.55*     | 5.40 ± 0.46*     | 5.57 ± 0.52*     |
| Body weight (kg)               | 69.05 ± 7.50     | 68.50 ± 7.32*    | 68.35 ± 7.05*    | 68.41 ± 6.98*    |

* Not significant.
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