Serum Lipoprotein Levels During Long-term Treatment of Hypertension with Indapamide

WOLFGANG MEYER-SABELLEK, REINHARD GOTZEN, JOERG HEITZ, HANS-RICHARD ARNTZ, AND KARL-LUDWIG SCHULTE

SUMMARY The beneficial effect of antihypertensive pharmacotherapy in decreasing morbidity and mortality in hypertensive patients may be counteracted by metabolic and biochemical disturbances, such as hypokalemia, hyperglycemia, hyperuricemia, and hyperlipoproteinemia, that occur with the administration of thiazides and related diuretics. Antiatherogenic high-density lipoprotein cholesterol may be unchanged, whereas the potentially atherogenic low-density lipoprotein cholesterol may be increased by long-term therapy with thiazide diuretics. Indapamide is a methylindoline antihypertensive diuretic with a considerable peripheral vasodilatory effect. At a low dose of 2.5 mg daily, it did not alter total circulating cholesterol, in contrast to chlorthalidone. High-density lipoprotein cholesterol levels increased significantly in 20 hypertensive men after 6 months of therapy with indapamide, resulting in a significant fall of the low-density lipoprotein/high-density lipoprotein ratio, an atherogenic risk factor, regardless of preexisting lipid disorders.

(Hypertension 7 [Suppl II]: II-170-II-174, 1985)

KEY WORDS • total body potassium • high-density lipoprotein cholesterol

MULTICENTER trials demonstrated the beneficial effect of antihypertensive pharmacotherapy in decreasing morbidity and mortality in patients with high blood pressure, including mild hypertension. Long-term antihypertensive therapy with thiazides and related diuretics has been associated with distinct biochemical side effects, including changes in total body potassium, hypokalemia, hyperglycemia, and hyperuricemia, and to a lesser degree, decreased glucose tolerance and worsening diabetes mellitus.

More recent studies focused on impaired lipid metabolism due to long-term therapy with sulfonamide diuretics. Weidmann et al. showed that hydrochlorothiazides and chlorthalidone increase plasma triglycerides and total cholesterol in mildly hypertensive patients. Other investigations also demonstrated a tendency to increased triglyceride and/or total cholesterol levels in patients treated with thiazide diuretics. Significant increase of the potentially atherogenic serum low-density lipoprotein (VLDL) cholesterol fractions may be detected with long-term treatment with thiazide diuretics, whereas the level of antiatherogenic high-density lipoprotein (HDL) cholesterol remains unchanged. It is therefore of considerable importance to study lipoproteins, which are probably more important correlates of atherogenesis than lipid levels per se with any long-term diuretic and/or antihypertensive therapy.

Miller et al. were among the first to note an inverse correlation between HDL cholesterol and the prevalence of coronary heart disease (CHD). Data generated from the Framingham Study showed that the cholesterol ratio (total cholesterol to HDL cholesterol) was higher among men and women with clinical evidence of CHD than among those with standard risk factors. Despite these data, information about effects of treatment with diuretics on serum lipoproteins has been limited to speculations in some studies.

Indapamide is an indole diuretic that is useful in the management of mild to moderate hypertension. The drug exerts its antihypertensive effect through a dual mechanism: volume contraction and direct reduction of vascular reactivity. It is well absorbed, extensively metabolized, and predominantly eliminated through biliary excretion.
Patients and Methods

We studied 20 men (ranging in age from 29-52 years) with mild to moderate essential hypertension (World Health Organization strata I and II), 7 of whom had preexisting hyperlipoproteinaemia (2 type IIb, 5 type IV), who had been referred to the outpatient clinic by local general practitioners. All antihypertensive treatment was stopped for at least 2 weeks and all diuretics for at least 4 weeks before the study. Patients with secondary hypertension, cardiac insufficiency, diabetes mellitus, and gout were excluded, as were alcoholics or patients receiving hormone treatment. Patients were advised to follow a regular diet and to consume no alcohol. Informed consent was obtained from each patient.

During the first 6 weeks, the patients received one placebo tablet each morning. During the next 6 months, the placebo was replaced by a tablet that looked exactly the same but contained 2.5 mg indapamide.

The following values were measured at the end of placebo therapy, and after 6 weeks and 6 months of indapamide therapy: plasma sodium, plasma potassium with a flame photometer, plasma creatinine with an autoanalyzer, uric acid in blood, glucose and glucose loading enzymatically, aldosterone excretion with radioimmunoassay by the method of Vecsei et al., total cholesterol enzymatically by the method of Roschlau et al., total triglycerides in the coupled enzymatic test according to Eggstein and Kreutz, and lipoproteins using ultracentrifugation according to the method of Hatch et al. The definition of hyperlipoproteinaemia and normal values of lipoproteins for the patients were those of Amtz. Total body potassium, with the °K method in the human body counter, was calculated in 11 patients and performed at the Institute of Radiology at Klinikum Steglitz. Using a standard cuff and sphygmomanometer, blood pressure was measured with patients recumbent (after 15 minutes) and standing (after 3 minutes). The pulse rate was taken at the same time. Statistical evaluation was done with the Friedman rank test and the Wilcoxon test. The median and variations were given for each group.

Results

Supine blood pressure fell significantly from a median of 160/105 mm Hg (Table 1) with placebo treatment to 145/95 mm Hg after 6 weeks and 140/90 mm Hg after 6 months of active treatment with indapamide. In the standing position, blood pressure declined from 160/105 after placebo treatment to 150/100 to 145/95 mm Hg after 6 months of active treatment with indapamide (Table 1). Changes in aldosterone excretion increased, but not significantly, from 29.9 μmol/24 hours to 47.6 after 6 weeks and 37.4 after 6 months. All patients demonstrated normal (to 5.44 mmol/L) fasting glucose levels. Three patients with increased glucose loading tests (normal after 120 minutes of 6.1 mmol/L) were not affected throughout therapy. A slight but not significant increase after 6 months of therapy provided no indication of impaired glucose tolerance (Table 2).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo</th>
<th>Indapamide 6 wk</th>
<th>Indapamide 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.3</td>
<td>3.9*</td>
<td>4.0†</td>
</tr>
<tr>
<td>Total body potassium (°K/body wt)</td>
<td>1.93</td>
<td>1.89</td>
<td>1.95</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>140</td>
<td>139</td>
<td>140</td>
</tr>
<tr>
<td>Aldosterone excretion (μmol/24 hr)</td>
<td>29.9</td>
<td>47.6</td>
<td>37.4</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>4.68</td>
<td>4.70</td>
<td>4.59</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>101</td>
<td>97</td>
<td>98</td>
</tr>
<tr>
<td>Uric acid (μmol/L)</td>
<td>385</td>
<td>410</td>
<td>392</td>
</tr>
</tbody>
</table>

*p < 0.01 6 wk vs placebo.
†p < 0.01 6 mo vs placebo.
‡p < 0.05.

| TABLE 1. Median and Range of Systolic (SBP) and Diastolic (DBP) Blood Pressure and Heart Rate (HR) Before (Placebo) and After Treatment |
|-----------------|-----------------|-----------------|
| Position        | Placebo         | Indapamide 6 wk | Indapamide 6 mo |
| SBP Supine      | 160 (140-105)   | 145* (120-160)  | 140† (125-160)  |
| DBP Upright     | 100 (95-115)    | 95* (90-105)    | 90† (80-100)    |
| SBP Upright     | 160 (140-195)   | 150t (140-170)  | 145† (125-170)  |
| DBP Upright     | 105 (95-120)    | 100 (80-115)    | 95† (85-100)    |
| HR Supine       | 72 (68-96)      | 80 (64-96)      | 76 (68-102)     |
| HR Upright      | 88 (74-108)     | 96 (72-116)     | 92 (80-112)     |
Table 3. Median and Range of Serum Cholesterol Before (Placebo) and After Treatment (Indapamide 2.5 mg/day)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Indapamide 6 wk</th>
<th>Indapamide 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total C</td>
<td>230 (169-316)</td>
<td>231 (167-504)</td>
<td>238 (169-368)</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>30 (9-106)</td>
<td>27 (6-184)</td>
<td>27 (8-156)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>158 (104-198)</td>
<td>164 (110-256)</td>
<td>153 (106-236)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>38 (26-54)</td>
<td>43 (25-64)</td>
<td>44* (24-62)</td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>3.86 (2.63-6.23)</td>
<td>3.71 (2.73-6.28)</td>
<td>3.61 (2.16-6.08)</td>
</tr>
</tbody>
</table>

Serum cholesterol (C) = mg/100 ml.  
*p < 0.05 6 mo vs placebo.

Table 3 demonstrates a slight but insignificant increase in total cholesterol with indapamide. All the individual values showed this rising trend irrespective of the presence of preexisting hyperlipidemia. Examining the lipoprotein fractions, one notices that LDL and VLDL cholesterol remained constant after 6 weeks and 6 months of indapamide therapy, whereas HDL cholesterol tended to increase. Thus the increase in total cholesterol can be attributed to the simultaneous increase in this fraction. In connection with a simultaneous significant increase in HDL triglycerides (Table 4), the increase in HDL cholesterol could imply an increase in the total amount of HDL. If one examines the LDL cholesterol/HDL cholesterol ratio and computes the so-called risk index according to Kostner, one can see that this ratio decreased from 3.86 to 3.71 after 6 weeks to 3.61 after 6 months (Figure 1).

Despite the percentage of patients who at the beginning had elevated triglyceride levels documented in the range (see Table 4), no significant change occurred in the median total triglyceride level after long-term therapy. There were marked variations in the individual triglyceride levels, especially in patients with prior hyperlipoproteinemia. A not unexpected result was the clear variation in the individual total triglyceride levels. These variations were reflected in the VLDL triglyceride concentrations, whereas the triglyceride concentrations of the LDL and HDL fractions, in accordance with their metabolic activity, showed only minor variations. Comparison of pretreatment and posttreatment values indicated a significant decline of LDL triglyceride and a significant increase of HDL triglyceride. It is safe to assume that drug-induced effects on lipid metabolism can be particularly well assessed in these patients. The elevated LDL/HDL quotient of 3.86 calculated for our patients before therapy can thus be explained by the makeup of the study group with its representative proportion of persons with lipometabolic disorders. The reduction of this quotient to 3.61 can be considered a further indication that this therapy has no negative effect on the lipid profile.

Discussion

Changes in lipid profile such as an increase of LDL cholesterol or a decrease in HDL cholesterol may increase the risk of CHD.\(^{16,17}\) It is considerably important to study the short- and long-term effects of antihypertensive therapy on lipid metabolism. In the present study, we investigated indapamide, a sulfonamide derivative, with both antihypertensive and diuretic properties at a low dose of 2.5 mg/day. Weidmann et al.\(^{18}\) studied the acute effect of indapamide on lipid profile after 6 weeks and found no apparent influence on serum lipids or lipoproteins in humans. Our observations after 6 weeks and 6 months in moderately hypertensive men confirmed these results, which were in contrast to

Table 4. Median and Range of Serum Triglycerides Before (Placebo) and After Treatment (Indapamide 2.5 mg/day)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Indapamide 6 wk</th>
<th>Indapamide 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Tg</td>
<td>134 (84-627)</td>
<td>132 (65-957)</td>
<td>127 (65-968)</td>
</tr>
<tr>
<td>VLDL-Tg</td>
<td>79 (27-487)</td>
<td>82 (18-767)</td>
<td>80 (20-875)</td>
</tr>
<tr>
<td>LDL-Tg</td>
<td>46 (22-97)</td>
<td>51 (27-129)</td>
<td>41* (21-75)</td>
</tr>
<tr>
<td>HDL-Tg</td>
<td>13 (1-43)</td>
<td>16 (2-60)</td>
<td>20† (4-50)</td>
</tr>
</tbody>
</table>

Serum triglyceride (Tg) = mg/100 ml.  
*\(p < 0.01\) 6 mo vs 6 wk.  
†\(p < 0.01\) 6 mo vs placebo.  
‡\(p < 0.05\) 6 mo vs placebo.

**Figure 1.** Difference to baseline data (after placebo) for LDL cholesterol, HDL cholesterol, and LDL/HDL cholesterol ratio after 6 weeks (left columns) and 6 months (right columns) of therapy with indapamide. *\(p < 0.05\) (6 mo vs placebo). †\(p < 0.05\) (6 mo vs 6 wk).
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those noted with various other commonly used diuretics. Whether or not elevation of serum LDL cholesterol levels during treatment with chlorthalidone or hydrochlorothiazide\textsuperscript{13} or elevation of beta-lipoprotein fraction during furosemide therapy\textsuperscript{14} will persist during long-term treatment and modify the coronary risk is presently unknown.

Our observations demonstrated an increase in the range of VLDL triglyceride. This could be due either to a higher rate of formation or to a reduced rate of disintegration. It may be speculated that indapamide, like other thiazide diuretics, increases cyclic adenosine 3’5’-monophosphate\textsuperscript{26} due to inhibition of phosphodiesterase, which stimulates lipolysis in fatty tissue.\textsuperscript{27} Free fatty acids would be released into the plasma and could be used for synthesis of VLDL in the liver.

Body weight, hematocrit, and plasma albumin levels remained unchanged throughout the study, indicating the minor role of volume contraction in lowering blood pressure. Potassium depletion with diuretic therapy may create a biologically insulinopenic state and may explain in part the known adverse effects of thiazide-induced lipid disorders.\textsuperscript{28} Despite a small but significant fall in levels of serum potassium, this study ruled out a potassium depletion using a total body counter.

Unchanged or even lower levels of total triglyceride and cholesterol in hypertensive men after 3 to 6 years of thiazide treatment have been reported.\textsuperscript{29,30} This might be related in part to dietary modification or handling and/or storing of samples.

The absence of lipoprotein alterations after long-term treatment with indapamide may be partially explained by the drug’s biochemical structure and the dosage used. Compared to the high daily doses of 100 mg chlorthalidone or hydrochlorothiazide administered in several studies,\textsuperscript{8,9,11,13} low-dose thiazides,\textsuperscript{21,32} that is, less than 12.5 mg daily, might possibly be as effective in antihypertensive therapy, as we demonstrated with 2.5 mg of indapamide, which caused fewer adverse metabolic consequences.\textsuperscript{20}

Acknowledgments

We are indebted to Professor P. Koepe for his invaluable help evaluating total body potassium. The authors are grateful to Mrs. A. Härtenerberger for her skillful technical assistance and Mrs. W. Kinst for preparing the manuscript.

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Hypertension. 1985;7:II170
doi: 10.1161/01.HYP.7.6_Pt_2.II170

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