Normalization of Lipid Metabolism after Withdrawal from Antihypertensive Long-term Therapy with Beta Blockers and Diuretics

Martin Middeke, Werner Oskar Richter, Peter Schwandt, Brigitte Beck, and Heinrich Holzgreve

Blood pressure and serum lipoprotein concentrations were assessed in 40 men with essential hypertension at the end of a long-term, controlled intervention study (HAPPHY) after 5.2±1.4 years of treatment with hydrochlorothiazide (n=23) or atenolol (n=17) and after a wash-out period. After withdrawal from antihypertensive medication, the blood pressures of patients treated with diuretics or beta blockers rose from 142/93 and 145/91 to 159/106 and 165/104 mm Hg, respectively. At the same time, low density lipoprotein cholesterol decreased by 17 and 12 mg/dl, respectively, in the diuretic and beta blocker groups (p<0.05). In addition, total cholesterol decreased by 16 mg/dl (p<0.05) in the diuretic group, whereas high density lipoprotein cholesterol increased by 8 mg/dl (p<0.01) and triglycerides decreased by 27 mg/dl (p<0.05) in the beta blocker group at the end of the wash-out period as compared to the final phase of the HAPPHY study. The data indicate the persistence of lipid changes during long-term treatment with hydrochlorothiazide and atenolol. For the first time, it was clearly demonstrated that the well-known unfavorable effects of diuretics and beta blockers on lipid metabolism are reversible after cessation of long-term therapy of several years’ duration.

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(Beta blockers and diuretics are recommended worldwide as first-line drugs for treatment of hypertension. Both drugs have adverse, but different, effects on lipid metabolism during long-term therapy.\(^1\)\(^2\)\(^3\)\(^4\) However, there have been no data on the persistence of the lipid changes during medication of several years’ duration. Furthermore, the effect on lipid metabolism of discontinuing beta blockers and diuretics after long-term administration had not previously been evaluated. Therefore, we measured the lipoprotein profile in patients from the HAPPHY study who had essential hypertension after their long-term antihypertensive therapy with atenolol and hydrochlorothiazide and again after medication was discontinued.

Methods

Patients

Forty men with essential hypertension who were participating in the HAPPHY study\(^*\) were randomly assigned to hydrochlorothiazide or atenolol medication according to the study protocol. All patients had been continuously treated with antihypertensives for several years. Their mean daily doses were 51.1±12.1 mg of hydrochlorothiazide in the diuretic group and 75.0±31.9 mg of atenolol in the beta blocker group. In addition, dihydralazine was given to seven patients in the diuretic group and to five in the beta blocker group. After antihypertensive medication was discontinued, a wash-out period of a minimum of 4 weeks with no treatment was instituted. Blood pressure was measured in all patients in the sitting position with a device that allows blind registration (Random Zero Sphygmomanometer, Hawksley & Sons Ltd., Lancing, England). Two readings 5 minutes apart were taken, and the mean of these is reported.

A special lipid-lowering diet was not considered to be necessary in these patients and was therefore not recommended. Consistent with normal medical practice, general advice was given concerning restriction of nicotine, alcohol, excessive salt, and calorie intake as appropriate during the HAPPHY study as well as after medical treatment was discontinued.

High density lipoproteins (HDL), low density lipoproteins (LDL), and triglycerides in serum were determined at the end of the HAPPHY study and at the end of the wash-out period. Cholesterol and triglycerides were measured enzymatically (Boehringer kits, Boehringer, Mannheim, FRG). HDL cholesterol was measured after precipitation of other serum lipoproteins with sodium phosphotungstate and magnesium chloride (Boehringer kit). LDL cholesterol was calculated according to the formula of Friedewald et al.\(^5\) when the triglyceride concentration did not exceed 400 mg/dl. Lipid assay procedures were standardized throughout the trials against reference material supplied by the National Center of Quality Control for Clinical Laboratories (INSTAND). Furthermore, all lipid values were determined in duplicate; values differed by no more than ±2% (SD).

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Results

After 5.2±1.4 years of antihypertensive treatment in the HAPPHY trial, blood pressure was 145/91±16/6 in patients treated with a diuretic and 142/93±14/6 mm Hg in patients treated with a beta blocker. During the wash-out period, blood pressure increased to 165/104±17/7 and to 159/106±16/7 mm Hg (p<0.001) after 4.6±1.5 weeks. Simultaneously, heart rate decreased from 79±6 to 75±6 (p=ns) in the diuretic group and increased from 75±6 to 74±7 beats/min (p<0.05) in the beta blocker group (see Table 1).

After medication with diuretics was discontinued, total cholesterol decreased from 247±39 to 231±35 mg/dl (p<0.05), and LDL cholesterol decreased from 167±35 to 150±43 mg/dl (p<0.05), whereas HDL cholesterol (46±17 and 45±17 mg/dl) and triglycerides (176±106 and 182±106 mg/dl) remained unchanged. Cessation of beta blocker treatment led to a decrease of LDL cholesterol from 162±44 to 150±35 mg/dl (p<0.05) and of triglycerides from 196±97 to 189±93 mg/dl (p<0.05), and to an increase in HDL cholesterol from 37±6 to 45±11 mg/dl (p<0.01). Additional therapy with dipyridamole had no significant influence on the lipoprotein changes, and there were no significant weight changes in either group.

Discussion

Since both beta blockers and diuretics, which are still the most widely recommended antihypertensive drugs, can adversely affect serum lipoprotein concentrations,1,2,3 there has been concern because of the possible repercussions on coronary heart disease. In fact, it has been shown in long-term trials that standard antihypertensive therapy has little or no preventive effect on coronary heart disease.4-9 There is uncertainty about the clinical consequences and the persistence of serum lipoprotein abnormalities induced by long-term antihypertensive medication. Possible explanations are that, in the long run, the pharmacologic effects on lipoproteins disappear or that dietary influences override any pharmacologic effect. The persistence of the lipid changes after several years of antihypertensive medication is unresolved. Furthermore, there are no data showing the effect on lipoproteins of discontinuing long-term antihypertensive therapy with beta blockers or diuretics.

Hypertensive patients who participated in the HAPPHY study provided a unique opportunity for us to observe the effects of long-term treatment and of then discontinuing antihypertensive therapy. The well-known adverse effects of atenolol (increase of triglycerides and decrease of HDL cholesterol) and of hydrochlorothiazide (increase of total and LDL cholesterol) which were described earlier in these patients1 persisted for more than 5 years as shown in our study. It was clearly shown during the wash-out period that the lipid changes were reversible after medication was discontinued. In addition, after the beta blocker was removed, there was a significant reduction of LDL cholesterol during the wash-out period, whereas we could not detect any increase in LDL cholesterol after beta blocker treatment began.1 This reduction may have been due to the greater number of observed patients (n=17) at the end of this study compared to the number (n=9) in our previous study. As was shown previously, additional therapy with dipyridamole in some patients in both treatment groups had no significant effect on lipid metabolism.1

The persistent effects of beta blockers and diuretics on lipid metabolism during long-term antihypertensive therapy of more than 5 years' duration could have clinical significance for coronary heart disease. With long-term antihypertensive treatment alone, there has been only a moderate reduction of coronary heart disease.10 One possible explanation of the results of the hypertension trials is that the drugs that were used induced metabolic side effects, which may have increased the risk of coronary heart disease. The benefit from antihypertensive therapy may be negated by increasing another risk factor (hyperlipoproteinemia) for coronary heart disease. Therefore, a strategy aimed at treating elevated blood pressure and keeping LDL cholesterol as low as possible seems to be more promising for the reduction of coronary heart disease. In addition, decreasing elevated triglycerides and increasing HDL cholesterol seems to be beneficial.11

Table 1. Characteristics of Hypertensive Men during Therapy and after a Wash-out Period

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HAPPHY trial (5.2±1.4 yrs)</th>
<th>Wash-out period (4.6±1.5 wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diuretic</td>
<td>Beta blocker</td>
</tr>
<tr>
<td>N</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Blood pressure, systolic/diastolic (mm Hg)</td>
<td>145/91±16/6</td>
<td>142/93±14/6</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>79±6</td>
<td>69±5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83±9</td>
<td>84±9</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>247±39</td>
<td>240±52</td>
</tr>
<tr>
<td>LDL chol (mg/dl)</td>
<td>167±35</td>
<td>162±44</td>
</tr>
<tr>
<td>HDL chol (mg/dl)</td>
<td>48±17</td>
<td>37±7</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>176±106</td>
<td>196±97</td>
</tr>
</tbody>
</table>

*p<0.001, †p<0.01, ‡p<0.05 compared to the HAPPHY trial.

Chol=cholesterol, LDL=low density lipoprotein, HDL=high density lipoprotein.

The diuretic used was hydrochlorothiazide; the beta-blocker was atenolol.

Statistical analysis was performed with Wilcoxon's signed rank test for matched pairs.
If drug therapy is introduced, the possible long-term unfavorable effects of beta blockers and diuretics on lipid metabolism have to be considered, especially in hypertensive persons who have concomitant hyperlipidemia. Blood lipids have to be monitored in all patients. On the other hand, it has to be taken into account that, in patients already under medication with beta blockers and diuretics, hyperlipidemia can be secondary (drug-induced), which implies a different therapeutic treatment.

From our results, we found that lipid changes with beta blockade and diuretics persisted for more than 5 years, and these changes may influence the course of coronary heart disease. However, the adverse effects of those drugs on lipid metabolism are fully reversible after medication is discontinued.

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Index Terms: serum lipoproteins • antihypertensive therapy • diuretics • beta blockers
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