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

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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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Statistical analysis was performed with Wilcoxon’s signed rank test for matched pairs.

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±8 (p<ns) in the diuretic group and increased from 69±5 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 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 169±93 mg/dl (p<0.05), and to an increase in HDL cholesterol from 37±7 to 45±11 mg/dl (p<0.01). Additional therapy with dihydralazine had no significant influence on the lipidoprotein 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 events.4-6-9 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 dihydralazine in some patients in both treatment groups had no significant effect on lipid metabolism.1

The persisting 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
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.

References
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