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Pravastatin Has an Additional Depressor Effect in Patients Undergoing Long-Term Treatment With Antihypertensive Drugs

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Background: Statins have been reported to have direct vascular effects independent of cholesterol reduction. To assess the antihypertensive effect of statins, a crossover study was designed to compare the depressor effect of pravastatin and probucol in hypertensive patients undergoing long-term treatment with antihypertensive drugs.

Methods: The subjects enrolled in this study were 52 hypertensive patients (22 men and 30 women, mean age 62.8 ± 9.3 years) who were treated with the same antihypertensive drugs for more than 1 year and had serum cholesterol levels of more than 5.69 mmol/L. In 26 subjects, pravastatin at a dose of 10 mg/d was given first for 6 months followed by treatment with probucol at a dose of 500 mg/d, and vice versa in the remaining 26 subjects. Serum lipids, apolipoproteins, glucose, and insulin were measured on the final day of the control period, and pravastatin and probucol treatments. The homeostatic model assessment insulin resistance index (HOMA-IR) was used to assess insulin resistance.

Results: The blood pressure decreased after pravastatin treatment (141.2 ± 4.7/81.3 ± 4.9 to 136.5 ± 5.3/80.6 ± 5.1 mm Hg, $P < .001$/.499), but did not decrease after probucol treatment (141.2 ± 4.7/81.3 ± 4.9 to 141.4 ± 4.9/80.8 ± 4.9 mm Hg, $P = .832$/.634). Total cholesterol decreased significantly after pravastatin (6.69 ± 0.69 to 5.23 ± 0.77 mmol/L, $P < .001$) and probucol treatment (6.69 ± 0.69 to 5.53 ± 0.64 mmol/L, $P < .001$). The HOMA-IR was decreased by probucol (1.92 ± 0.78 to 1.57 ± 0.59, $P = .029$), whereas pravastatin had no effect on HOMA-IR.

Conclusions: It can be concluded that the depressor effect of pravastatin may have an additional benefit in the treatment of hypertensive patients with hyperlipidemia without any adverse effect on insulin sensitivity. Am J Hypertens 2004;17:502–506 © 2004 American Journal of Hypertension, Ltd.

Key Words: Pravastatin, probucol, crossover trial, insulin resistance.

Statins have been reported to have direct vascular effects independent of cholesterol reduction.[1,2] Antihypertensive effects of statins have been reported in Dahl salt-sensitive rats[3,4] and spontaneously hypertensive rats.[5] In addition to animal models of hypertension, several reports confirmed a significant reduction in blood pressure (BP) associated with the use of statins in patients with untreated hypertension,[6–8] even in patients with normal lipid levels.[9] Two reports noted that the use of statins in combination with antihypertensive drugs could improve BP control in patients with uncontrolled hypertension.[10,11] Conversely, other studies on well-controlled hypertensive patients were unable to demonstrate a BP-lowering effect of statins.[12–15]

To assess the antihypertensive effect of statins, a crossover study was designed to compare the depressor effect of pravastatin and probucol in hypertensive patients undergoing long-term treatment with antihypertensive drugs.

Methods

Subjects

This study was conducted on 52 Japanese subjects (22 men and 30 women; mean age, 62.8 years; range, 38 to 81 years) with moderate, established primary hypertension who were treated with the same antihypertensive drugs for more than 1 year and had serum cholesterol levels of more

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than 220 mg/dL (5.69 mmol/L). All female patients included in this study were menopausal with an age range of 54 to 74 years. Subjects with secondary hypertension or with diabetes mellitus, as diagnosed according to the glucose criteria of the World Health Organization (WHO) Consultation (fasting plasma glucose levels ≥7.0 mmol/L, 2 h after glucose load ≥11.2 mmol/L),[16] were excluded from the study. Clinical information about the subjects was obtained from their medical records, which included the duration of hypertension and antihypertensive medication, family history of hypertension and diabetes mellitus, daily alcohol intake, and tobacco consumption. Estimated duration of hypertension and antihypertensive medication were 13.7 ± 7.7 years (range, 3 to 38 years) and 8.3 ± 5.4 years (range, 2 to 22 years). Thirty-one subjects (59.6%) had a family history of hypertension, but only 2 subjects exhibited a family history of diabetes mellitus. Fifteen subjects ingested alcohol every day and 10 subjects were smokers. Thirteen patients were treated with diuretics (indapamide and mefruside), 31 patients were treated with β-blockers (atenolol), 31 patients were treated with calcium channel blockers (nitrendipine and manidipine), and 2 patients were treated with angiotensin-converting enzyme inhibitors (captopril and lisinopril).

The nature of the study and potential risk associated with it were explained to all subjects, who gave their written informed consent before participating in the study. The study protocol was approved by the Institutional Review Board on Human Investigations of NTT Kanto Medical Center and Shounan Kamakura General Hospital.

Study Design

The study was a randomized, open, controlled 2×2 crossover trial[17] in which the two treatments were pravastatin and probucol. It consisted of a 6-month run-in period with antihypertensive medication, a 6-month active treatment period with pravastatin or probucol (period 1), a 1-month washout period, and a 6-month treatment period with the alternative treatment (period 2). At the end of the run-in period, subjects were randomized to one of the two sequences: pravastatin/probucol (sequence 1) or probucol/pravastatin (sequence 2). Pravastatin at a dose of 10 mg/d and probucol at a dose of 500 mg/d were used during each treatment period. The subjects were asked to adhere strictly to their food habits and maintain a healthy lifestyle. To evaluate the add-on effects of pravastatin and probucol, all antihypertensive drugs were kept constant throughout the study. Blood was collected at baseline and at the end of both treatment periods, after a 12-h fast, for lipids, apolipoprotein (Apo) A1 and B, creatinine, uric acid, glucose, glycated hemoglobin A_{1c} (HbA_{1c}), insulin, β-2 microglobulin (β-2 MG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatine kinase (CK).

BP Measurements

Blood pressure and pulse rate were measured every 4 weeks at the hypertension clinic of both hospitals. Blood pressure and pulse rate were measured by averaging the last three of five readings taken with an automatic blood pressure monitor (TM-2540C; A & D, Tokyo, Japan) in the sitting position at each 1-month outpatient clinic visit by the nursing staff. Blood pressure values used for analysis were the average of data obtained during the last 3 months of the run-in period, and pravastatin and probucol treatments.

Biochemical Analysis

Serum cholesterol and triglycerides were measured by an enzymatic technique with an automatic analyzer (model H 736; Hitachi, Tokyo, Japan). High-density lipoprotein cholesterol was measured after precipitation of LDL, very low-density lipoprotein, and chylomicron with dextran sulfate, magnesium chloride, and polyethylene glycol. The LDL cholesterol was calculated using Friedewald's formula.[18] Apo A1 and Apo B were measured by turbimetric immunoassay with APO A-1 AUTO-N DAIICHI and APO B AUTO-N DAIICHI (Daiichi Pure Chemicals, Tokyo, Japan). The coefficient of variation was 3.4% for Apo A1 and 3.5% for Apo B. Plasma glucose was measured by the glucokinase method on an automatic analyzer. HbA_{1c} was measured by high performance liquid chromatography. The serum level of insulin was determined by competitive enzyme immunoassay with a double antibody procedure using EIA Test Insulin II [BMY] (Boehringer Mannheim, Mannheim, Germany). Homeostasis model assessment insulin resistance index (HOMA-IR) was calculated by the formula glucose (in millimoles per liter) × insulin (in microunits per milliliter)/22.5.[19] Serum β-2 MG was measured by the latex agglutination method using the β-2-M-2 kit (Eiken Kagaku, Tokyo, Japan). Serum creatinine, uric acid, transaminases ALT and AST, and CK were measured by an automatic analyzer. Predicted creatinine clearance was calculated using the formula of Cockcroft and Gault.[20]

Statistical Analysis

All data in the text and tables are mean ± standard deviations of the mean (SD). Crossover analysis of variance was used to test carryover effects of treatment.[17] One-way analysis of variance and Fisher's protected least significance difference were used for analyzing the difference of data at baseline and each treatment period when no carryover effect was observed. The Pearson product moment formula was used for calculation of coefficients of correlation between changes of BP and serum lipids after pravastatin and probucol treatment. All statistical analyses were performed using SPSS software, version 11.5 (SPSS Inc., Chicago, IL).

Table 1. Baseline characteristics of subjects received pravastatin first (sequence 1) and probucol first (sequence 2) and all subjects combined

Variable	Sequence 1 (n = 26)	Sequence 2 (n = 26)	All Subjects (n = 52)
Men/women	11/15	11/15	22/30
Age (y)	65.0 ± 9.7	60.7 ± 8.5	62.8 ± 9.3
Body length (cm)	153.6 ± 8.0	154.4 ± 7.0	154.2 ± 7.6
Body weight (kg)	56.6 ± 9.0	60.5 ± 8.7	58.7 ± 8.9
Body mass index (kg/m^2)	24.0 ± 3.1	25.4 ± 3.2	24.7 ± 3.2
Alcohol use	8 (30.8%)	7 (26.9%)	15 (28.8%)
Tobacco use	6 (23.1%)	4 (15.4%)	10 (19.2%)
Antihypertensives used			
Number	1.65 ± 0.80	1.27 ± 0.45*	>1.46 ± 0.67
Diuretics	8 (32.0%)	5 (18.5%)	13 (25.0%)
β-blockers	16 (61.5%)	15 (57.7%)	31 (59.6%)
Calcium channel blockers	17 (65.4%)	14 (53.8%)	31 (59.6%)
ACE inhibitors	2 (7.7%)	0 (0%)	2 (3.8%)

Values are mean ± SD.
* $P < .05$ compared with sequence 1.

Results

All patients completed the study without any significant adverse reactions. Baseline characteristics of subjects were similar regardless of which drug they had been randomized to receive first, pravastatin (sequence 1) or probucol (sequence 2), except the number of antihypertensive drugs used per patient (Table 1). There were no carryover effects in all measured variables (all t <0.269).

Table 2 presents the changes in BP and laboratory parameters after pravastatin and probucol treatments. Body weight and body mass index were stable throughout the study. Systolic BP decreased significantly by 4.7 mm Hg after pravastatin treatment, but remained unchanged after probucol treatment. No significant changes from baseline were observed for diastolic BP with pravastatin or probucol treatment. Pravastatin treatment caused a decrease in pulse pressure of 4.0 mm Hg.

Both pravastatin and probucol treatments decreased total and LDL cholesterol and Apo B. The effects of both treatments were comparable. The HDL cholesterol and Apo A1 were not changed by pravastatin, but decreased with probucol. Serum insulin levels were decreased by 17.3% with probucol, but were not changed by pravastatin. Because the two drugs did not affect plasma levels of glucose, HOMA-IR was decreased by 18.2% with probucol indicating that probucol induced improvement of insulin resistance.

No statistically significant correlations were found between changes in total and LDL cholesterol and changes in systolic BP after pravastatin treatment (Δtotal cholesterol versus Δsystolic BP, $r = 0.067$, $P = .637$, ΔLDL cholesterol versus Δsystolic BP, $r = 0.220$, $P = .116$) or probucol treatment (Δtotal cholesterol versus Δsystolic BP, $r = 0.223$, $P = .111$, ΔLDL cholesterol versus Δsystolic BP, $r = 0.160$, $P = .256$).

No patient reported musculoskeletal symptoms. The CK values were not changed after pravastatin or probucol treatment. Transaminases tended to increase with pravastatin, whereas no change was observed with probucol. Although the changes of transaminases or CK were not statistically significant, increases in transaminases and CK were observed in a few cases after pravastatin or probucol treatment. Transaminases were increased by more than 10 IU/L in 8 cases (15.3%) with pravastatin and in 2 cases (3.8%) with probucol. The incidence of the increase in transaminases was higher with pravastatin treatment than with probucol treatment ($P = .039$). The CK values were increased by more than 50 IU/L in 2 cases (3.8%) and in 1 case (1.9%) with pravastatin and probucol, respectively. Serum creatinine, estimated creatinine clearance, and uric acid were not changed by either pravastatin or probucol treatment.

Discussion

In our selected patients whose BPs were moderately controlled, pravastatin significantly decreased systolic BP associated with a significant decrease in total cholesterol. On the other hand, probucol showed no significant changes in BP, despite the fact that the decrease in total cholesterol induced by probucol was the same as that induced by pravastatin. Previous studies confirmed that statins had a BP-lowering effect in untreated hypertensive patients with hypercholesterolemia.[6–8] The reduction of BPs showed a poor correlation with changes in plasma lipids. Moreover, the antihypertensive effect was seen even in isolated hypertensive patients with normal lipid levels.[9] These results suggest that the antihypertensive effect of statins seen in untreated hypertensive patients is independent of their lipid-lowering effect. Studies that included normotensive individuals whose systolic BP was less than 122 mm Hg[21–23] or well-controlled hypertensive patients whose

Table 2. Changes of blood pressure and laboratory parameters after pravastatin and probucol therapy

Variable	Treatment			*P*		
	Baseline	Pravastatin	Probucol	Baseline versus Pravastatin	Baseline versus Probucol	Pravastatin versus Probucol
Systolic blood pressure (mm Hg)	141.2 ± 4.7	136.5 ± 5.3	141.4 ± 4.9	< .001	.832	< .001
Diastolic blood pressure (mm Hg)	81.3 ± 4.9	80.6 ± 5.1	80.8 ± 4.9	.499	.634	.841
Pulse pressure (mm Hg)	59.9 ± 6.4	55.9 ± 6.3	60.6 ± 5.3	< .001	.571	< .001
Pulse rate (beats/min)	63.1 ± 5.2	63.0 ± 3.6	63.1 ± 4.0	.947	.943	.891
Total cholesterol (mmol/L)	6.69 ± 0.69	5.43 ± 0.77	5.23 ± 0.64	< .001	< .001	.153
HDL cholesterol (mmol/L)	1.34 ± 0.38	1.38 ± 0.34	0.97 ± 0.25	.823	< .001	< .001
LDL cholesterol (mmol/L)	4.47 ± 0.77	3.17 ± 0.74	3.45 ± 0.74	< .001	< .001	.058
Triglycerides (mmol/L)	2.01 ± 1.45	2.01 ± 1.34	1.82 ± 1.12	.997	.442	.444
Apolipoprotein A1 (g/L)	1.45 ± 0.24	1.47 ± 0.27	1.14 ± 0.21	.641	< .001	< .001
Apolipoprotein B (g/L)	1.40 ± 0.27	1.20 ± 0.36	1.20 ± 0.22	< .001	< .001	.981
Glucose (mmol/L)	5.32 ± 0.49	5.34 ± 0.50	5.30 ± 0.61	.914	.829	.746
Hemoglobin A1c (%)	5.15 ± 0.41	5.23 ± 0.43	5.17 ± 0.39	.331	.785	.486
Insulin (μg/mL)	8.07 ± 3.07	8.16 ± 3.48	6.67 ± 2.35	.8815	.026	.018
HOMA-IR	1.92 ± 0.78	1.94 ± 0.88	1.57 ± 0.59	.868	.029	.019
AST (IU/L)	23.3 ± 8.5	25.6 ± 9.4	23.5 ± 6.9	.171	.943	.192
ALT (IU/L)	22.6 ± 14.0	24.7 ± 13.8	22.9 ± 11.7	.409	.911	.475
CK (IU/L)	124.0 ± 68.0	124.6 ± 63.1	115.0 ± 61.4	.964	.482	.459
Creatinine (μmol/L)	73.3 ± 17.9	73.1 ± 20.7	69.8 ± 21.3	.962	.379	.406
β2-microglobulin (mg/L)	1.54 ± 0.3	1.45 ± 0.69	1.46 ± 0.63	.463	.539	.901
Predicted Ccr (mL/min/1.73 m^2)	80.4 ± 22.2	79.6 ± 20.8	86.6 ± 27.3	.874	.177	.132
Uric acid (μmol/L)	335.1 ± 95.1	334.7 ± 88.4	336.2 ± 89.8	.979	.954	.933

Values are mean ± SD

HDL = high-density lipoprotein; LDH = low-density lipoprotein; HOMA-IR = homeostasis model assessment insulin resistance index; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CK = creatine kinase; Ccr = creatinine clearance.

systolic BP was less than 135 mm Hg[12–15] were unable to demonstrate the BP-lowering effect of statins. These findings suggest that statins have no depressor effect in subjects with normal or controlled systolic BP of less than 135 mm Hg.

On the other hand, two case-controlled studies demonstrated the add-on effect of statins in treated hypertensive patients. In a case controlled study by Spósito et al[10] on 31 treated hypertensive patients, 20 mg/d lovastatin or 10 mg/d pravastatin, decreased systolic and diastolic BP by 23 mm Hg and 19 mm Hg, respectively, in hypertensive patients treated with angiotensin-converting enzyme inhibitors enalapril or lisinopril. In an observational study on 127 hypertensive patients with hypercholesterolemia by Borghi et al,[11] the use of pravastatin or simvastatin in combination with various antihypertensive drugs was associated with a greater reduction in both systolic and diastolic pressure than that obtained with antihypertensive treatment alone. The patients investigated in these two reports had BP levels of 153 ± 9/100 ± 3 mm Hg and 161 ± 21/94 ± 9 mm Hg. Generally speaking, decreases in BP by statins seem to be related to pretreatment BP levels. Statins had no antihypertensive effect in normotensive individuals or in patients with well-controlled BP levels, whereas statins showed a significant BP-lowering effect in patients with poorly controlled BP. The patients in this study had BP moderately controlled with various antihypertensive drugs at an average systolic BP of 141 mm Hg. We observed significant reduction of systolic BP by 4.7 mm Hg using a strictly controlled crossover protocol and obtained clinical evidence of the add-on antihypertensive effect of pravastatin in moderately controlled hypertensive patients. Further data are awaited on the issue of whether statins had an antihypertensive effect in subjects with high-normal systolic BP between 135 and 140 mm Hg. Additional evidence obtained in this study indicated that pravastatin had no effects on serum levels of glucose or insulin. However, probucol decreased serum insulin by 17.3% without a change in glucose, which resulted in 18.2% reduction of HOMA-IR. Although the mechanism by which probucol improved insulin sensitivity is not clear, Yasunari et al[24] reported that probucol improved impaired insulin-mediated glucose uptake in cultured rabbit coronary smooth muscle cells by reduction of intracellular oxidative stress. The clinical implication of these findings is that this mechanism has the potential to im-

prove insulin sensitivity in humans. As far as we are aware, no reports concerning the effect of probucol on insulin sensitivity have appeared and the findings in this study provide the first clinical evidence that probucol improves insulin sensitivity in hypertensive patients undergoing long-term antihypertensive drug treatment.

Although statins have been reported to improve endothelial function in spontaneously hypertensive rats through the same superoxide dismutase–mediated antioxidant effect[25] as that of probucol,[26] pravastatin had no favorable effect on insulin sensitivity that differed from the effect of probucol in our study. Previous studies in which the effect of statins on insulin sensitivity was examined in patients with type 2 diabetes mellitus had variable results.[27–29] Further clinical studies using the glucose clamp method are required to clarify the exact effect of lipid-lowering drugs on glucose metabolism.

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