Effects of Atorvastatin and Pravastatin on Malondialdehyde-Modified LDL in Hypercholesterolemic Patients

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The aim of the present study was to compare the effects of atorvastatin and pravastatin on lipid parameters and the concentration of malondialdehyde-modified low-density lipoprotein (MDA-LDL) in hypercholesterolemic patients. A total of 17 patients (10 men, 7 women; mean age, 68 ± 9 years) who were indicated for drug therapy based on the National Cholesterol Education Program II underwent an 8-week regimen of atorvastatin (10 mg/day) or pravastatin (10 mg/day) with a 4-week washout period between drugs. After an overnight fast, lipid parameters and MDA-LDL concentration were measured before and after the 8-week treatment with each drug. Both atorvastatin and pravastatin produced significant reductions in low-density lipoprotein (LDL) cholesterol and MDA-LDL concentrations, with a significant increase in high-density lipoprotein cholesterol concentration. The percent reductions in LDL cholesterol and MDA-LDL concentration were significantly greater with atorvastatin than pravastatin ($46 \pm 6\%$ vs $24 \pm 10\%$, $p < 0.0001$, and $44 \pm 10\%$ vs $14 \pm 13\%$, $p < 0.0001$, respectively). The ratios of percent reductions in MDA-LDL concentrations and percent reductions in LDL cholesterol concentrations were significantly greater for atorvastatin than pravastatin (0.96 ± 0.19 vs 0.59 ± 0.55 , $p < 0.0001$). In conclusion, atorvastatin reduced serum concentrations of LDL cholesterol and MDA-LDL to a greater degree than pravastatin, indicating that atorvastatin not only has stronger lipid-lowering effects, but also stronger antioxidative effects than pravastatin. (*Circ J* 2003; 67: 816–820)

Key Words: Hypercholesterolemia; Oxidized low-density lipoprotein; Statins

Oxidized low-density lipoprotein (LDL) plays a key role in the initiation and development of atherosclerosis through a variety of effects, such as recruitment of monocytes, adhesion of leukocytes to endothelial cells, promotion of intraluminal thrombosis, activation of lymphocytes, enhanced cytotoxicity, and impairment of endothelium-dependent vasorelaxation.^{1–4} It has become possible to measure the serum concentrations of oxidized LDL or malondialdehyde-modified LDL (MDA-LDL)^{5–11} and their circulating concentrations have been reported to be significantly higher in patients with coronary artery disease (CAD) than in controls.^{9–11} Sasaki et al reported that atorvastatin decreased the serum concentration of MDA-LDL in patients with mixed hyperlipoproteinemia¹² and although atorvastatin produces greater reductions in the serum concentrations of total and LDL cholesterol than other statins, such as simvastatin, pravastatin, lovastatin, and fluvastatin,¹³ it is unclear whether this statin has more effect on decreasing the serum concentrations of MDA-LDL than other statins. In the present study, we compared the effects of atorvastatin and pravastatin on the serum concentrations of MDA-LDL in hypercholesterolemic patients.

Methods

Study Population

The study patients consisted of 17 patients (10 men, 7

women; mean age, 68 ± 9 years) who were indicated for drug therapy based on the National Cholesterol Education Program II.¹⁴ Exclusion criteria were: (1) use of anti-inflammatory or lipid-lowering drugs or antioxidant supplements, (2) currently smoking, (3) renal or liver dysfunction, (4) diabetes mellitus, (5) the presence of angina attacks, (6) a history of stroke or acute coronary syndrome within 6 months, (7) a history of coronary interventional therapy within the past year, (8) chronic heart failure, (9) collagen disease, infection, malignant diseases, or recent (<6 months) major surgery or trauma, and (10) change in the drugs administered within the 3 months prior to registration in the study.

Study Protocol

The study protocol is shown in Fig 1. It was a randomized crossover design and the study started 1 month after registration. The patients underwent an 8-week regimen of statin therapy of either atorvastatin (10 mg/day) or pravastatin (10 mg/day) with a 4-week washout period between drugs. The study protocol was in agreement with the guidelines of the institutional ethics committee and informed consent was obtained from each patient prior to enrollment in the study.

After an overnight fast, venous blood samples were obtained before and after the 8-week treatment with atorvastatin or pravastatin. The concentrations of LDL cholesterol, triglycerides, and HDL cholesterol were assayed by enzymatic methods. Serum concentrations of MDA-LDL were measured using an enzyme immunoassay kit (SRL, Inc, Tokyo, Japan). Intra- and inter-assay variations were within 3.5% and 6.9%, respectively.

Statistical Analysis

All data are expressed as means $\pm$ SD. Paired t test was

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Fig 1. Study protocol.

Table 1 Patient Characteristics

<i>n</i>	17
Age, years	68±9
Male (%)	10 (59%)
Ex-smoker (%)	10 (59%)
Hypertension (%)	13 (76%)
Coronary artery disease (%)	15 (88%)
Old cerebral infarction (%)	1 (6%)
ACE inhibitors (%)	2 (12%)
Calcium antagonists (%)	12 (71%)
-blockers (%)	4 (24%)
Aspirin (%)	14 (82%)

ACE, angiotensin-converting enzyme.

used to compare the differences between the data before and after the 8-week treatment with atorvastatin or pravastatin. The Pearson's correlation analysis was performed to estimate correlations between the concentrations of MDA-LDL and LDL cholesterol, triglyceride, or HDL cholesterol. A *p* value <0.05 was considered statistically significant.

Results

Patient characteristics are shown in Table 1. Of the 17 patients studied, there was a history of smoking and hypertension in 10 (59%) and 13 (76%), respectively. Fifteen patients (88%) had CAD, but because of previous percutaneous transluminal coronary intervention, none of the patients experienced anginal attacks during the study. Angiotensin-converting enzyme inhibitors, calcium channel antagonists, -blockers, and aspirin were currently being administered to 2 (12%), 12 (71%), 4 (24%), and 14 (82%) patients, respectively.

Fig 2 shows the relationship between the serum concentrations of MDA-LDL and those of LDL cholesterol, triglycerides and HDL cholesterol. MDA-LDL tended to correlate positively with LDL cholesterol and triglycerides ($r=0.43$, $p=0.08$, and $r=0.46$, $p=0.06$, respectively). There was no significant correlation between the serum concentrations of MDA-LDL and HDL cholesterol ($r=-0.15$,

Fig 2. Relation of serum concentration of malondialdehyde-modified low-density lipoprotein (MDA-LDL) to those of LDL cholesterol, triglyceride, or HDL cholesterol.

$p=0.56$).

Table 2 shows the lipid parameters and MDA-LDL concentrations before and after the 8-week treatment with either atorvastatin or pravastatin. Both statins produced significant reductions in the serum concentrations of LDL cholesterol and MDA-LDL, with a significant increase in that of HDL cholesterol. Serum concentrations of triglycerides were significantly reduced only by atorvastatin. Fig 3 shows the percent reductions in lipid parameters and MDA-LDL concentrations by the 8-week treatments. Percent reductions in serum concentrations of LDL cholesterol and MDA-LDL were significantly greater with atorvastatin than pravastatin ($46\pm6\%$ vs $24\pm10\%$, $p<0.0001$ and $44\pm10\%$ vs $14\pm13\%$, $p<0.0001$, respectively). The percent reductions in LDL cholesterol and MDA-LDL by pravastatin did not differ significantly between patients administered the drug initially and those who received it after the cross-over ($24\pm11\%$ vs $24\pm11\%$ and $14\pm11\%$ vs $14\pm15\%$, respectively) nor was there any significant difference for the patients who were given atorvastatin ($45\pm7.5\%$ vs $47\pm4.5\%$ (initial treatment) and $42\pm10\%$ vs $46\pm11\%$ (after cross-over), respectively). The ratios of percent reductions in MDA-LDL concentrations and percent reductions in LDL cholesterol concentrations were significantly greater for atorvastatin than pravastatin (0.96 ± 0.19 vs 0.59 ± 0.55 , $p<0.0001$) (Fig 4). Percent reductions in triglyceride concentrations tended to be greater with atorvastatin than pravastatin ($26\pm21\%$ vs $8.9\pm28\%$, $p=0.053$). The percent increases in HDL cholesterol did not differ significantly between atorvastatin and pravastatin ($10\pm14\%$ vs $9.8\pm14\%$).

No adverse effects were observed in any patients.

Table 2 Changes in Serum Lipid Parameters and MDA-LDL Concentrations Before and After Treatment With Atorvastatin and Pravastatin

	Atorvastatin		<i>p</i> value	Pravastatin		<i>p</i> value
	Before	After		Before	After	
LDL cholesterol, mg/dl	150±26	80±18	<0.0001	149±26	112±17	<0.0001
MDA-LDL, U/L	157±49	85±20	<0.0001	147±36	123±27	0.0015
Triglycerides, mg/dl	102±46	69±24	0.0007	84±31	76±35	0.15
HDL cholesterol, mg/dl	57±12	63±12	0.0017	58±13	63±13	0.11

Data are presented as mean ± SD. LDL, low-density lipoprotein; MDA, malondialdehyde-modified; HDL, high-density lipoprotein.

Fig 3. Percent reductions in serum concentrations of LDL cholesterol, MDA-LDL, and triglycerides after 8-week treatment with atorvastatin or pravastatin.

Discussion

In the present study, both atorvastatin and pravastatin decreased LDL cholesterol and MDA-LDL concentrations in hypercholesterolemic patients, but these effects were significantly greater with atorvastatin. These results indicate that atorvastatin not only has stronger lipid-lowering effects but also stronger antioxidant effects than pravastatin.

In hypercholesterolemic patients, the concentration of circulating LDL is increased, and the LDL is more aged and more susceptible to oxidative modifications than LDL from healthy subjects.¹⁵ Indeed, in the present study, serum MDA-LDL concentrations tended to correlate positively with those of LDL cholesterol. Therefore, the greater reduction in the serum MDA-LDL concentrations by atorvastatin might result from the greater reduction in serum LDL cholesterol. Because 'aged' LDL is more prone to oxidative processes during its long presence in the circulation, a substantial removal of 'aged' LDL via increased LDL receptor activity, mainly in the liver, could contribute to a

Fig 4. Ratios of percent reductions in serum concentration of MDA-LDL and percent reductions in LDL-cholesterol concentration after 8-week treatment with atorvastatin or pravastatin.

reduction in the susceptibility of the 'new' LDL population in the circulation to oxidation,¹⁶ leading to the reduced levels of circulating MDA-LDL. However, the ratios of percent reduction in MDA-LDL and LDL cholesterol were significantly greater for atorvastatin than pravastatin, which suggests that with atorvastatin other mechanisms independent of the LDL cholesterol-lowering effect contribute more to the reduction in serum MDA-LDL concentration. The para- and ortho-hydroxymetabolites of atorvastatin, but not the parent compound, possess antioxidative properties¹⁷ and the protective effect of these hydroxymetabolites against the oxidation of LDL may have led to the greater decrease in MDA-LDL.

Statins have been shown to exert antioxidant effects by reducing the expression of essential NAD(P)H oxidase subunits that are the predominant source of reactive oxygen species in the vessel wall.¹⁸ However, it is unclear whether this effect contributes to the reduction in circulating MDA-LDL concentrations.

Endothelial dysfunction is an initiating factor in the development of atherosclerosis¹⁹ and oxidized LDL evokes endothelial dysfunction by impairing the signal transduction between endothelial cell surface receptors and nitric oxide production,²⁰ inhibiting nitric oxide synthase expression,^{21,22} increasing the oxidative degradation of nitric oxide,²³ and inducing apoptosis.²⁴⁻²⁶ Oxidized LDL also disturbs vasomotion by direct interaction with vascular smooth muscle cells.²⁷ We previously reported that there was a significant correlation between the plasma concentrations of oxidized LDL and the coronary vasomotor response to acetylcholine in patients with stable CAD,²⁸ which suggested that the circulating oxidized LDL concentration may indirectly reflect the impairment of endothelium-dependent vasodilation. Zhu et al demonstrated that atorvastatin reduces the concentration of lysophosphatidylcholine in oxidized LDLs, leading to improved endothelium-depen-

dent relaxation of blood vessels.²⁹ Given recent observations that endothelial dysfunction predicts future atherosclerotic disease and cardiovascular events,^{30,31} a reduction in the serum concentration of MDA-LDL which is a major component of oxidized LDLs, may reduce the likelihood of future atherosclerotic disease and cardiovascular events. Indeed, a recent study reported that the concentration of circulating oxidized LDL is an important predictor for cardiac events in patients with CAD.³² Further studies are needed to clarify whether, because of its greater lipid-lowering and antioxidative effects, atorvastatin is the more advantageous than other statins in the management of hypercholesterolemic patients.

Study Limitations

First, the number of patients studied was small and therefore, large population studies are needed to confirm our results. Second, the frequency of patients with CAD was extremely high and therefore, our results cannot be generalized to all patients with hypercholesterolemia. The status of CAD could affect the serum concentration of MDA-LDL; Holvoet et al have shown that plasma concentrations of MDA-LDL were significantly higher in patients with acute coronary syndrome.⁹ However, in the present study, none of the patients had experienced acute coronary syndrome within the 6 months prior to the study. Third, 13 (76%) of the present patients were being treated with angiotensin-converting enzyme inhibitors and/or calcium channel antagonists, which could affect the concentration of MDA-LDL.^{33,34} However, these treatments were started at least 3 months prior to registration, and their dosages were not changed within 3 months of registration or during the study. Therefore, we do not believe that these drugs strongly affected our results.

Conclusions

Atorvastatin reduced the serum concentrations of LDL cholesterol and MDA-LDL to a greater degree than pravastatin, indicating that it not only has stronger lipid-lowering effects but also stronger antioxidative effects than pravastatin. Further studies will be needed to clarify whether atorvastatin is the more advantageous drug for the management of hypercholesterolemic patients.

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