Effect of Pravastatin and Atorvastatin on Glucose Metabolism in Non-Diabetic Patients with Hypercholesterolemia

Michiro Ishikawa¹, Atsushi Namiki¹, Tetsuya Kubota¹, Suguru Yajima¹, Masayuki Fukazawa¹, Masao Moroi¹ and Kaoru Sugi¹

Abstract

Objective The aim of this study was to assess the effects of hydrophilic pravastatin and lipophilic atorvastatin on glucose metabolism and lipid metabolism in non-diabetic patients with hypercholesterolemia.

Methods Fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels were determined before and after statin treatment.

Patients A total of 44 non-diabetic patients (FPG ≤ 125 mg/mL; HbA1c < 5.8%) undergoing treatment with either pravastatin (n=21) or atorvastatin (n=23) for hypercholesterolemia were investigated.

Results FPG level in the pravastatin but not atorvastatin group was significantly lowered after vs before treatment. Accordingly, the HbA1c level in the atorvastatin but not in the pravastatin group was significantly increased. As expected, both TC and LDL-C levels were significantly lowered in both groups. In particular, the TC level in the atorvastatin group was more remarkably and significantly improved than in the pravastatin group. On the other hand, the HDL-C level in the pravastatin group but not in the atorvastatin group was significantly increased after the administration period. The TG level was unaffected in both groups.

Conclusion Pravastatin was suggested to act favorably, while atorvastatin adversely, regarding its effects on glucose metabolism in non-diabetic hypercholesterolemic patients, although atorvastatin exerted more potent cholesterol-lowering effects compared with pravastatin.

Key words: pravastatin, atorvastatin, glucose metabolism, lipid metabolism

(DOI: 10.2169/internalmedicine.45.1476)

Introduction

The West of Scotland Coronary Prevention Study (WOSCOPS) emphatically demonstrated that cardiovascular events can be prevented by treatment with pravastatin, a 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin) (1). It is well documented that the primary effects of statins are to block endogenous synthesis of cholesterol and to reduce low-density lipoprotein cholesterol (LDL-C) and intermediate-density lipoprotein cholesterol levels by up-regulation of LDL receptors in the liver (2).

Many patients with hyperlipidemia develop complications of diabetes mellitus, which may include “metabolic syndrome”, visceral obesity, and hypertension. Hence stringent lipid management is necessary for hyperlipidemic patients with complications of diabetes mellitus. Although statins play a central role in the management of hyperlipidemia, consistent data on the effects of these drugs on controlling patients’ blood glucose levels have not been thus far obtained (3, 4).

Therefore, we retrospectively assessed the effects of a hydrophilic statin, pravastatin, and a lipophilic statin, atorvastatin, on glucose metabolism in non-diabetic patients with hy-
Figure 1. (A) : Fasting plasma glucose (FPG) level (mg/dL) at baseline (Pre) and after the treatment with pravastatin or atorvastatin (Post). *: p=0.015 vs Pre. (B) : Difference in FPG levels (mg/dL) between before and after the treatment (Post-Pre). The p value in (B) was obtained by comparing the differences of FPG levels between baseline and after the treatment with pravastatin and atorvastatin.

Figure 2. (A) : Hemoglobin A1c (HbA1c) level (%) at baseline (Pre) and after the treatment with pravastatin or atorvastatin (Post). **: p<0.0001 vs Pre. (B) : Difference in HbA1c levels (%) between before and after the treatment (Post-Pre). The p value in (B) was obtained by comparing the differences of HbA1c levels between the baseline and after the treatment with pravastatin and atorvastatin.

Table 1. Baseline Characteristics of the Study

<table>
<thead>
<tr>
<th></th>
<th>Pravastatin</th>
<th>Atorvastatin</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>21</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>69±2</td>
<td>72±2</td>
<td>0.67</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>129/107</td>
<td>106/133</td>
<td>0.37</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (71)</td>
<td>16 (70)</td>
<td>0.61</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>14 (67)</td>
<td>16 (70)</td>
<td>0.84</td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>11</td>
<td>8</td>
<td>0.25</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>9</td>
<td>12</td>
<td>0.38</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>6</td>
<td>8</td>
<td>0.70</td>
</tr>
<tr>
<td>Diuretics</td>
<td>3</td>
<td>6</td>
<td>0.34</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>219±4</td>
<td>255±6</td>
<td>0.16</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>131±5</td>
<td>142±4</td>
<td>0.33</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>55±3±3.8</td>
<td>61±4±4.5</td>
<td>0.21</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>174±9±23</td>
<td>163±18±6</td>
<td>0.78</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>109±3±76</td>
<td>114±6±42</td>
<td>0.33</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.9±0.1</td>
<td>5.6±0.1</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SE or n. Parenthesis indicates percent (%).
ACE-I: angiotensin-converting enzyme inhibitors, ARB: angiotensin II receptor blockers

Results

Background of the Patients

Among 44 hypercholesterolemic subjects enrolled in the present study, a total of 21 and 23 patients were treated with pravastatin (pravastatin group) and atorvastatin (atorvastatin group), respectively. Baseline characteristics of patients in the two groups were well matched. As summarized in Table 1, the average age of patients in the pravastatin group was 69±2 years, while that in the atorvastatin group was 72±2 years. In addition, no statistically significant difference was observed in the ratio of male to female patients and in the rate of complication of hypertension or ischemic heart diseases in the two groups. The ratios of patients who took ACE inhibitors or angiotensin II receptor blockers, calcium channel blockers, beta blockers and diuretics were not significantly different. Furthermore, the plasma levels of TC, LDL-C, HDL-C, TG, FPG, and HbA1c in both groups were not significantly different.

FPG and HbA1c Levels

Comparing the pre- and post-treatment value, FPG the level was significantly (p=0.015) reduced in the pravastatin group, while that in the atorvastatin group was not significantly different (Fig. 1A). However, the average differences of FPG levels after the treatment from their baseline levels

Patients and Methods

A total of 44 non-diabetic patients with hypercholesterolemia who visited the Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, Tokyo, Japan from January 2002 through February 2004 were enrolled. Patients were treated with either pravastatin (5 to 10 mg, mean 8.9±2.1 mg) or atorvastatin (5 to 10 mg, mean 8.2±2.4 mg) for hypercholesterolemia. The status of non-diabetes mellitus in the present study was defined based on the criteria of the American Diabetic Association: a fasting plasma glucose (FPG) level of less than 125 mg/mL (5), and hemoglobin A1c (HbA1c) level of less than 5.8%. The levels of FPG, HbA1c in plasma, and total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), triglyceride (TG) in serum were determined before and after treatment with either pravastatin or atorvastatin for an average period of 9.7±0.7 months. Diet therapy and exercise therapy were not significantly different in the period. Informed consent was obtained from all patients. The Committee on Clinical Research of Toho University Ohashi Medical Center approved the study protocol.

All results are expressed as mean±SE. Statistical analysis was conducted by Student’s t test. A value of p<0.05 was defined as statistical significance.
TC, LDL-C, HDL-C, and TG Levels

Both TC and LDL-C levels in the pravastatin and atorvastatin group were significantly decreased below their baseline levels (Fig. 3A and Fig. 4A). However, the difference between their baseline level and the average level after the treatment in the atorvastatin group was significantly (TC, $p=0.0255$; LDL-C, $p=0.0287$) greater than those in the pravastatin group (Fig. 3B and Fig. 4B).

On the other hand, the HDL-C level in the pravastatin group but not in the atorvastatin group was significantly (p<0.0001) increased over the baseline level (Fig. 5A). The average difference of HDL level in the pravastatin group tended to be increased (p=0.073) compared from that in the atorvastatin group (Fig. 5B).

TG levels were unaffected in both groups, although the level in the pravastatin group tended to be decreased (Fig. 6A). The differences between baseline and post-treatment levels in the two groups were not significantly different (Fig. 6B).
Discussion

The present study was conducted in non-diabetic patients with hypercholesterolemia. In these patients, the FPG level was significantly decreased in the pravastatin group but not in the atorvastatin group, while the HbA1c level was significantly increased in the atorvastatin group and remained unaltered in the pravastatin group. Furthermore, the difference in the HbA1c level after the treatment from the baseline level was significantly increased in the atorvastatin group, but not in the pravastatin group. From these results, it was suggested that treatment with atorvastatin, contrary to pravastatin, adversely affects glucose metabolism in non-diabetic patients.

On the other hand, analysis of TC and LDL-C levels before and after treatment with either statin suggested that atorvastatin was significantly more potent than pravastatin in improving these parameters. HDL-C levels, however, showed better improvement in the pravastatin group compared with the atorvastatin group.

Although there are several reports describing the effects of statins on glucose metabolism, such effects seem variable from statin to statin. Furthermore, even within the same statin, inconsistent effects have been reported according to different studies. For instance, in a subanalysis of normoglycemic patients enrolled in WOSCOPS (1), among those who subsequently went on to develop diabetes mellitus during the follow-up period of 4.9 years, 30% fewer were in the pravastatin arm than in the placebo arm (6). On the other hand, the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) study in patients at high risk of cardiovascular diseases revealed that the number of patients treated with atorvastatin who newly became diabetic during the study was marginally increased compared with in the placebo group (7). However, in the Collaborative Atorvastatin Diabetes Study (CARDS), multicentre randomised placebo-controlled trial, in which the subjects were patients with type 2 diabetic mellitus, changes of HbA1c levels in patients on atorvastatin did not differ from those in the placebo group (8). In addition, the Heart Protection Study (HPS) revealed that the incidence of de novo patients with diabetes in individuals at high risks in the simvastatin group was slightly increased compared with that in the placebo group (9). Furthermore, in the PROVE-IT TIMI 22 Substudy (10), atorvastatin significantly increased the HbA1c level in non-diabetic patients compared with pravastatin.

At least 3 possibilities have been suggested as preventing mechanisms of pravastatin against risk of developing diabetes mellitus: TG-lowering effect of pravastatin may possibly contribute to the prevention of development of diabetes, since there are numerous reports of an association between high plasma TG levels and the development of this condition; pravastatin inhibits the production of proinflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 (11), which may cause metabolic syndrome and insulin resistance (12); and pravastatin is reported to improve endothelium-dependent coronary vasomotion (13), which may in turn lead to increased transport of glucose and insulin to peripheral tissues and thereby inhibit progression of insulin resistance.

Pravastatin is hydrophilic, while atorvastatin is lipophilic. Lipophilic statins exhibit direct effects on cells in vivo, unlike hydrophilic statins, and this may help explain their adverse effects on glucose metabolism in cells. For instance, hydrophilic statins show greater hepatoselectivity than lipophilic statins (14); hence lipophilic statins may be incorporated into many tissues other than the liver including the spleen, adipose tissues, and muscles and thereby may decrease insulin secretion and exacerbate insulin resistance. As specific mechanisms for this, several proposals have been put forward. In normal rat islets, lipophilic lovastatin reduced glucose-induced insulin secretion by inhibiting prenylation of GTP-binding proteins (15). Statins inhibit biosynthesis of isoprenoid, which is synthesized via the mevalonate pathway, and inhibit the biosynthesis of coenzyme Q10 (16). Thus the rate of ATP synthesis in pancreatic β-cells is slowed, possibly impairing insulin secretion. Furthermore, since lipophilic simvastatin but not hydrophilic pravastatin has been shown to block L-type calcium channels in pancreatic β-cells (17), there is a strong possibility that the lipophilic statins as a whole may prevent insulin secretion, which results from glucose-induced increase of intracellular calcium concentration as the initial step.

In conclusion, pravastatin was suggested to have beneficial effects, while atorvastatin adversely affects glucose metabolism in non-diabetic hypercholesterolemic patients, although atorvastatin exerted more potent cholesterol-lowering effects than pravastatin.

References

stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomized controlled trial. Lancet 361: 1149-1158, 2003.


