Effect of Pravastatin on Plasma Ketone Bodies in Diabetics with Hypercholesterolemia

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SUGIMURA, K. and FUKUDA, M. Effect of Pravastatin on Plasma Ketone Bodies in
—— Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) is a common intermediate
metabolite of cholesterol synthesis and ketone formation in the liver. In order
to study the effect of HMG-CoA reductase inhibitor (pravastatin) on ketone
formation, changes in the plasma levels of ketone bodies by treatment with
pravastatin were studied in 18 non-insulin dependent diabetics with hyperchole-
sterolemia. Body mass index, diabetic control, and plasma free fatty acid levels
were not changed during the study, and the plasma levels of cholesterol decreased
significantly from 250±25 to 211±34 mg/100 ml after 6 months of pravastatin
treatment. The plasma levels of acetoacetic acid also significantly decreased from
37.7±22.6 to 28.4±13.4 μmol/l, and those of 3-hydroxybutyric acid and total
ketone bodies also tended to decrease after pravastatin treatment. These results
suggest that pravastatin decreases ketone formation in hepatic mitochondria
besides cholesterol synthesis in hepatic microsome. ——— pravastatin; ketone
bodies; cholesterol; diabetes mellitus © 1998 Tohoku University Medical Press

Carbohydrate metabolism is closely related to lipid metabolism, and diabetes mellitus is frequently associated with hyperlipidemia and also hyperketonemia. Both cholesterol and ketone bodies are synthesized mainly in the liver, and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) is an intermediate metabolite in biosynthesis pathway of both of them.

Pravastatin is selectively transported into hepatocyte through carrier mediated pathway (Komai et al. 1992), and decreases sterol biosynthesis by inhibiting the enzyme to reduce HMG-CoA to mevalonic acid in hepatic microsomes (Tsujita et al. 1986; Koga et al. 1990, 1992; Parker et al. 1990), which may influence on

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ketone bodies formation from HMG-CoA in the hepatic mitochondria. However, it is not clear yet whether pravastatin has any effect on ketone formation which may be enhanced especially in diabetes mellitus. This study was undertaken to clarify effects of pravastatin on plasma levels of ketone bodies in the diabetics.

**Subjects and Methods**

Pravastatin was administered to 18 non-insulin dependent diabetics with hyperlipidemia, 15 males and 3 females aged 45 to 82 years with mean of 66.2 years, for a period of 6 months at a daily dose of 10 to 20 mg. They were on diet therapy without hypoglycemic agents. The initial plasma levels of total cholesterol and triglyceride were $250 \pm 25$ mg/100 ml and $164 \pm 130$ mg/100 ml, respectively.

In order to investigate the effects of pravastatin on plasma ketone bodies, fasting plasma levels of free fatty acid, acetoacetic acid and hydroxybutyric acid as well as those of fasting plasma glucose, immunoreactive insulin, HbA$_{1c}$, total cholesterol, triglyceride, high density lipoprotein (HDL)-cholesterol were measured before and 6 months after the treatment with pravastatin.

Plasma cholesterol and triglyceride were measured by automated enzymatic methods. HDL-cholesterol was measured enzymatically in the supernatant fluid after precipitation of low density lipoprotein (LDL) and very low density lipoprotein (VLDL) with heparin-calcium and nickel. Acetoacetic acid and 3-hydroxybutyric acid were measured enzymatically using 3-hydroxybutyrate dehydrogenase, and HbA$_{1c}$ by high-performance liquid chromatography.

Comparison between data before and after pravastatin treatment was made with paired $t$-test. $p$ Values $< 0.05$ were considered statistically significant.

**Results and Discussion**

Body mass index was not changed during the study. The HbA$_{1c}$, fasting plasma glucose levels and immunoreactive insulin were not influenced by pravastatin treatment (Table 1). The effect of pravastatin on serum lipids is shown in Table 2. The plasma levels of cholesterol and triglyceride were decreased after the treatment with pravastatin, and there was statistically significant change in the level of total cholesterol. The plasma levels of HDL-cholesterol showed tendency to increase. Those of acetoacetic acid, 3-hydroxybutyric acid and total

<p>| Table 1. Body mass index, plasma glucose, IRI and HbA$_{1c}$ before and 6 months after administration of pravastatin |
|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>BMI (kg/m$^2$)</th>
<th>Blood glucose (mg/100 ml)</th>
<th>IRI ($\mu$U/ml)</th>
<th>HbA$_{1c}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>24.0$\pm$3.2</td>
<td>141$\pm$23</td>
<td>5.71$\pm$2.77</td>
</tr>
<tr>
<td>After treatment</td>
<td>23.6$\pm$3.2</td>
<td>140$\pm$20</td>
<td>4.88$\pm$2.31</td>
</tr>
</tbody>
</table>
Pravastatin and Ketone Metabolism

Table 2. Changes in plasma lipid by treatment with pravastatin

<table>
<thead>
<tr>
<th></th>
<th>TC (mg/100 ml)</th>
<th>TG (mg/100 ml)</th>
<th>HDL-C (mg/100 ml)</th>
<th>FFA (mEq/l)</th>
<th>AAA (μmol/l)</th>
<th>3-HBA (μmol/l)</th>
<th>Total ketone bodies (μmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>250 ± 25</td>
<td>164 ± 130</td>
<td>54.9 ± 13.3</td>
<td>0.661 ± 0.128</td>
<td>37.7 ± 22.6</td>
<td>79.9 ± 61.0</td>
<td>124.7 ± 81.0</td>
</tr>
<tr>
<td>After treatment</td>
<td>211 ± 34*</td>
<td>125 ± 98</td>
<td>57.8 ± 10.8</td>
<td>0.674 ± 0.229</td>
<td>28.4 ± 13.4*</td>
<td>59.2 ± 56.3</td>
<td>82.5 ± 70.2</td>
</tr>
</tbody>
</table>

Data are mean ± s.d.

*P < 0.001

TC, Total cholesterol; TG, Triglyceride; HDL-C, HDL-cholesterol; FFA, Free fatty acid; AAA, Acetoacetic acid; 3-HBA, 3-Hydroxybutyric acid.

ketone bodies also decreased after pravastatin treatment, and there was significant difference in the levels of acetoacetic acid. No significant change was observed in those of free fatty acid.

It has been shown that pravastatin is selectively transported into hepatocytes through the carrier mediated pathway (Komai et al. 1992) and exhibits hepatocyte-selective inhibition of sterol synthesis (Tsujita et al. 1986; Koga et al. 1990, 1992; Parker et al. 1990), and pravastatin treatment reduces the serum cholesterol levels significantly in diabetes and non-diabetes (Nakaya et al. 1986; Yoshino et al. 1986; Hunninghake 1990; Kjaer et al. 1992).

Liver is the main organ to synthesize ketone bodies as well as cholesterol, and HMG-CoA is a common intermediate metabolite in both of cholesterol and ketone biosynthesis pathways. The reduction in plasma cholesterol levels by pravastatin treatment is thought to result from inhibition of HMG-CoA reductase. Decrease in reduction of HMG-CoA to mevalonate may increase ketone bodies formation from HMG-CoA in hepatic mitochondria.

There have been no data concerning the effect of pravastatin on ketone metabolism, and the present study reports comparison of plasma ketone levels before and after pravastatin treatment for the first time. Though the plasma levels of total cholesterol was significantly reduced by 20% after pravastatin treatment, plasma levels of ketone bodies did not increase but decreased after treatment with pravastatin. There was no relation between changes in plasma levels of total cholesterol and ketone bodies.

The plasma levels of insulin and free fatty acids have a great influence on ketone metabolism (McPherson et al. 1958; McGarry and Foster 1980), and synthesis of ketone bodies is enhanced in poorly controlled diabetes. The influence of HMG-CoA reductase inhibitors on glucose metabolism has not been consistently found. Zhang et al. (1995) reported that neither HbA1c nor fasting blood glucose changed significantly after pravastatin treatment. Sheu et al. (1994) reported that day-long plasma glucose concentration and insulin resistance were moderate-
ly, but significantly, greater after pravastatin treatment. Paolillo et al. (1991) reported that simvastatin, lipid soluble HMG-CoA reductase inhibitor, reduced the plasma levels of glucose and free fatty acid as well as cholesterol and triglyceride, and improved insulin action in elderly non-insulin dependent diabetes. In this study, the plasma levels of insulin was not changed by treatment with pravastatin. Their diabetes was fairly controlled in this study, and neither fasting plasma glucose nor HbA1c changed after treatment with pravastatin. Furthermore, though the plasma level of triglyceride showed tendency to be decreased by the treatment with pravastatin, that of free fatty acid showed no difference. These results suggest that decrease in the plasma levels of ketone bodies, which were demonstrated in this study, could not be explained by changes in diabetic control or plasma levels of free fatty acid.

It was reported that simvastatin, lipid soluble HMG-CoA reductase inhibitor, effects on the mitochondrial respiratory chain in the heart (Ichihara et al. 1993; Satoh et al. 1995), and that both simvastatin and pravastatin enhance the ischaemia-induced worsening of mitochondrial respiration in rat liver (Satoh et al. 1994). The present data may suggest that pravastatin also goes into liver mitochondrias, and changes ketone bodies formation from HMG-CoA.

These results suggest that pravastatin decreases the plasma levels of ketone bodies, and it is safely used for hypercholesterolemia in the diabetics in this respect. Further study is needed to elucidate the mechanism of decrease in plasma ketone bodies by pravastatin treatment.

References


