Effects of simvastatin on lipid levels and platelet activation in elderly patients with hypercholesterolemia

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Background and Objective To investigate the effects of simvastatin on lipid lowering therapy and platelet activation in elderly patients with hypercholesterolemia. Methods Fasting serum lipids, CD_63, CD_41a, serum glucose, hepatic and renal function, routine urine analysis (UA) were measured in 50 healthy subjects, and in 50 elderly patients with hypercholesterolemia before and after 4 weeks treatment with simvastatin (20mg daily for 4 weeks). Results 1. After simvastatin treatment for 4 weeks, the fasting serum level of lipids in elderly patients with hypercholesterolemia was significantly lower than before treatment (P<0.01). 2. CD_63 and CD_41a were decreased after treatment compared with before, respectively (1.36 0.34) vs (4.26 1.06), (P<0.01) and (123.54 19.73) vs (253.78 16.75), (P<0.01). 3. Changes in serum lipid level tended to be positively correlated with the declines in CD_63 and CD_41a, but there was no statistical significance (P>0.05). Conclusions The results suggested that lipid lowering therapy with simvastatin inhibit platelet activity. (J Geriatr Cardiol 2007;4:215-217.)

Key Words simvastatin; platelet activity; hypercholesterolemia

Introduction

According to large scale multi-centered studies, statins can significantly reduce plasma total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), and triglycerides (TG); they can also raise high density lipoprotein cholesterol (HDL-C), and dramatically decrease the morbidity and mortality in patients with cardiovascular disease. Because the occurrence and severity of cardiac events are positive to the level of activated platelets, we can dynamically monitor the lysosomal GP_3 (CD_63) and platelet membrane glycoprotein (CD_41a) to reflect the function of activated platelets by testing the fluorescent-signed monoclonal antibody and using flow cytometry. The purpose of our research is to explore the effect of simvastatin on serum lipids and the function of activated platelets in elderly patients who have abnormal serum lipid.

Methods

Study subjects

From Dec. 2004 to Oct.2005, we enrolled 50 patients with hypercholesterolemia to the study group, according to one of the following criteria: 1) If there were no other risk factors for coronary artery disease (CAD): TC>6.24mmol/L (240mg/dl), LDL-C 4.16 mmol/L (160mg/dl). Among them, 35 were male, 15 were female, with mean age of 66.1±5.6 years.

The patients with CAD, hypertension, thyroid gland disease, diabetes, dysfunction of platelets and blood coagulation, hepatorenal disease, and cancer were excluded. Other exclusion criteria were: 1) cerebrovascular disease, major wound or surgery in the last 6 months, 2) currently taking medicines such as anticoagulants, calcium channel blockers, or aspirin, which affect lipid and platelet activity, 3) pregnancy and 4) allergy to statins.

At the same time, 50 healthy adults, identified through physical examination, were selected as control. Thirty two were male, 18 were female, with mean age of 65.2±6.7. There was no significant difference in the baseline characteristics between the two groups.

Study protocol

The study patients were given simvastatin (Zocor, provided by MSD Corporation), 20mg every night. Fasting serum lipids, CD_63, CD_41a, glucose, liver and kidney function, and blood and urine values were measured at the beginning and at the 4th week follow-up in both groups.

The patients continued to take other medicines which do not affect lipid metabolism and platelet activation. Their diet and lifestyle were kept unchanged during the study period.

For serum lipids testing: TC and TG were measured by
the way of enzyme points destination and clearance methods to test HDL-C and LDL-C. This was strictly tested according to the handbook.

For CD\textsubscript{63}, CD\textsubscript{41a} testing: 1-2ml of blood was drawn with sodium citrate solution’s anti-coagulated vacuum tubes and measured immediately by flow cytometry(TASCAlibur, USA).

Other testings (blood and urine, and liver and kidney function), were performed by usual standards (Beckman Coulter, USA).

**Statistical analysis**

SPSS 11.0 statistical software was applied for statistical analysis. The data are described as and statistically calculated through ANOVA and linear correlation analysis. In all instances, P value of <0.05 was considered to be significant, and P value of <0.01 was considered very significant.

**Result**

The changes of lipid and platelet activity were shown in Table 1. The decline in lipids had a positive tendency but no significant correlation with the decrease in CD\textsubscript{63} and CD\textsubscript{41a} (r=0.125-0.201, P>0.05). The adverse effects of simvastatin were low, including one case of dizziness and mild nausea in the treatment group. Other clinical indexes (hepatorenal function, blood sugar, blood and urine routine analysis) had no significant change compared with the control group.

**Discussion**

With global aging accelerating, the morbidity of elderly Chinese patients with cardiovascular diseases is continually growing. It is proven that long-term high levels of TC, TG, and LDL-C, and low levels of HDL-C are responsible for the development of coronary heart disease and arteriosclerosis. So keeping TC, TG, LDL-C, and HDL-C at an appropriate level will help to prevent the progression of arteriosclerosis, reduce the size of atherosclerotic plaque, decrease major cardiovascular adverse events, and improve the patient’s survival. Current research showed that simvastatin reduced the level of TC, TG, and LDL-C. There are also little side effects, so that the benefits of statins outweigh their risks.

In general, most platelets are in quiescent state while only a minority are activated and in circulation. Stimulated by physiologic or physical factors, platelets could be largely activated. The quantity, type, and biological activity of membrane glycoprotein of the activated platelet will change, and then the adhesive, collective, and release function of platelets would change to abnormal. The major function of the platelet is hemostasis and thrombosis. It also takes part in the development of atherosclerosis. Platelet activity is elevated in hypercholesterolemic patients, who tend to present with cardiovascular diseases. Surfaces of static platelets do not have CD\textsubscript{63} protein, which is a lysosomal membrane protein. When a platelet is activated, lysosomal membranes would integrate to the neutrophil membrane. The activated platelet surface has the CD\textsubscript{63} protein which can induce adherence between the neutrocyte and activated endodermis membrane. Therefore, CD\textsubscript{63} is a particular indicator of activated platelets. CD\textsubscript{41a} is a GP\textsubscript{6b/5a} component of the intact GP\textsubscript{6b/5a} vitronectin, and thrombin sensitive protein. CD\textsubscript{41a} can introduce platelet agglomeration by binding of fibrinogen. This research indicates that the levels of CD\textsubscript{63} and CD\textsubscript{41a} significantly decrease, and the level of serum lipids also declines after patients have taken simvastatin for 4 weeks. This indicates that simvastatin could inhibit platelet activity, which is consistent with other clinical trials data. Its mechanism is still unclear; however, it may be related to the effect on serum lipids regulation as well as other regulations. Hypercholesterolemia could injure the structure and function of endodermis and collagen, which facilitates adherence and activation of platelets exposed after injury. Serum lipid regulation by simvastatin could reduce the endodermis injury. Simvastatin also increases the biological activity of nitrous oxide, and thus improves the endodermis function and platelet activity. In addition, simvastatin has an anti-inflammatory quality, inhibiting endothelium hyperplasia and stabilizing arteriosclerotic plaque.

It has been reported that the chemical structure of

<table>
<thead>
<tr>
<th>Group</th>
<th>Lipid(mmol/L)</th>
<th>Platelet activity</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>TC</td>
<td>TG</td>
</tr>
<tr>
<td>Study group (n=50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>6.65±0.12 *</td>
<td>2.15±0.39 *</td>
</tr>
<tr>
<td>After treatment</td>
<td>4.72±0.38 **</td>
<td>1.78±0.31 **</td>
</tr>
<tr>
<td>Control group (n=50)</td>
<td>4.52±0.46</td>
<td>1.58±0.28</td>
</tr>
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</table>

Note:* P<0.05, ** P<0.01, Compared with control group; *P<0.05, ** P<0.01, Compared with the group before treatment.
statins has some effect on platelet activation. Our study demonstrated that the tendency of platelet activation became worse while serum lipids became better; however, there was no relationship between them. This suggests that there be no relationship between serum lipid level and platelet activity, which is consistent with other relative references. It is presumed that the platelet activity lowering be related to the drug.

It can be deduced that simvastatin could reduce platelet activity while effectively regulating serum lipids, postponing the progression of cardiovascular and cerebral vascular diseases, and preventing the occurrence of thrombosis.

References