Benefits and Adverse Effects of Statins, Atorvastatin Calcium Hydrate, Pitavastatin Calcium, and Pravastatin Sodium, for Dyslipidemia in Patients on Hemodialysis

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Abstract

Objective: Risk factors development are similar to those implicated in cardiovascular diseases (cardiac failure, ischemic heart disease, and peripheral arterial disease), hypertension, diabetes mellitus, and dyslipidemia in hemodialysis (HD). Therefore, it is necessary to optimize the treatment (dyslipidemia) of these patients.

Methods: We examined changes in physiological parameters, renal function markers and lipid profiles induced by statins, such as pravastatin sodium (water-soluble, PS), atorvastatin calcium hydrate (fat-soluble, ACH) and pitavastatin calcium (fat-soluble, PC).

Results: Dyslipidemia with medication was observed in 34 (24.8%) of the 137 HD patients. The therapeutic statins used for dyslipidemia were as follows: PS was used in the nine patients, ACH was used in 11 patients and PC was used in nine HD patients. The waist circumference and body mass index were more significantly increased in the patients treated with ACH (90.9 ± 10.5 cm [mean ± standard deviation], 24.8 ± 2.9 kg/m²) than in the patients treated with PS (79.9 ± 10.3 cm, 21.0 ± 2.9 kg/m²; P < 0.05). While the serum triglyceride levels in the PS group were 103 ± 36 mg/dl, those in the ACH group were 164 ± 75 mg/dl (P < 0.05). In addition, the serum whole parathyroid hormone levels were significantly higher in the ACH group (151 ± 102 pg/ml) than in the PS group (59 ± 32 pg/ml; P < 0.05). There were no differences between the PS and the PC groups in any of the laboratory data, except for the serum creatinine levels.

Conclusion: Waist circumference, body mass index and the serum triglyceride levels were increased in the ACH HD patients. Interestingly, the serum whole PTH levels were found to be significant in the ESRD patients treated with ACH. Based on our results, PC may be an ideal statin for treating HD patients.

Keywords: Dyslipidemia; End-stage renal disease; Hemodialysis; Parathyroid hormone; Statins

Introduction

The development of hemodialysis (HD) has enabled patients with end-stage renal disease (ESRD) to survive for long periods. However, the progression of cardiovascular disease remains a major clinical problem. Consequently, dyslipidemia is common [1], and the presence of cardiovascular disease has become an increasingly important factor with regard to mortality in HD patients [2,3].

Chronic kidney disease (CKD) is associated with a significant burden of cardiovascular disease risk factors [4]. The prevalence of dyslipidemia in CKD patients is much higher than that observed in the general population whilst elevated cholesterol and triglyceride levels are associated with more rapid deterioration of the kidney function [5].

In this study, we evaluated the efficacy of treatment for dyslipidemia using statins in ESRD patients on maintenance HD. The purpose of the present report was to compare the lipid profiles and obesity parameters after treatment with statins, such as atorvastatin calcium hydrate (strong, fat-soluble; ACH), pitavastatin calcium (strong, fat-soluble; PC) and pravastatin sodium (regular, water-soluble; PS) in ESRD patients on HD.

Materials and Methods

Patients

A total of 137 patients (male/female, 92/45; age 60.8 ± 14.4 years [the mean ± standard deviation (SD)]) with ESRD on maintenance HD at Fukumitsu Hospital were examined.

Dyslipidemia with medication was observed in 34 (24.8%) of the 137 patients. We examined changes in physiological parameters, renal function markers and lipid profiles induced by statins, 3-hydroxy-3-methylglutary coenzyme A reductase inhibitors, such as PS, ACH and PC. The distribution of statins used for dyslipidemia among the 29 patients (male/female, 15/14; age 62.0 ± 12.4 years) on maintenance HD was as follows: ACH was used in 11 HD patients (7/4, chronic glomerulonephritis five, diabetic nephropathy four and polycystic kidneys disease two patients, 5.7 ± 2.3 mg), PC was used in nine HD patients (4/5, chronic glomerulonephritis four, diabetic nephropathy five patients, 1.1 ± 0.6 mg) and PS was used in nine HD patients (4/5, chronic glomerulonephritis two, diabetic nephropathy five and polycystic kidneys disease two patients, 6.7 ± 2.5 mg).

Following the introduction of HD at Kyushu University Hospital, Kyushu Medical National Hospital and Fukuoka Red Cross Hospital etc., HD patients were transferred to our hospital. No changes were made in the type or dose of medicines used to treat dyslipidemia at our hospital. As the statins had been used previously and the exact duration was not understood, this study did not include the baseline characteristics of the ESRD patients. Therefore, as a limitation, variables measured at baseline were not compared among the HD patients.

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The present study was performed using a non-randomized analysis at a single center with a retrospective and non-controlled design including a small number of patients. The procedures were carried out in accordance with the ethical standards of the committee on human experimentation at Fukumitsu Hospital.

**Dialysis schedule**

The patients underwent four- to five-hour sessions of HD therapy three times per week. We used a standard hollow-fiber dialyzer and bicarbonate, as follows: Na\(^+\) 140 mEq/L, K\(^+\) 2.0 mEq/L, Ca\(^++\) 2.5 mEq/L, Mg\(^+\) 1.0 mEq/L, Cl\(^-\) 110 mEq/L, CH\(_{3}\)COOH 8 mEq/L, HCO\(_3\)\(^-\) 30 mEq/L, and glucose 150 mg/dl in dialysate AF-3E. The blood flow rate was 200 ml/min, and the dialysate flow rate was kept constant at 500 ml/min.

**Physiological study**

In all patients, blood pressure before and after HD was routinely examined according to the Riva-Rocci method to screen for complications associated with maintenance HD. In this study, the body mass index (BMI) was simultaneously examined as the "dry weight" (body weight immediately after the HD) (kg)/height \(^2\) (m\(^2\)). Waist circumference and pelvic circumference were also measured.

**Blood sampling**

The hemoglobin, serum creatinine, blood urea nitrogen, calcium, phosphate, whole parathyroid hormone (PTH) (chemiluminescent enzyme immunoassay), blood glucose (postprandial blood glucose), hemoglobin A\(_1\)c (HbA\(_1\)c; National Glycohemoglobin Standardization Program; NGSP), low-density lipoprotein cholesterol (LDL-C) (direct method), high-density lipoprotein cholesterol (HDL-C) (direct method), triglyceride (TG) (enzyme method), albumin, uric acid, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, lactate dehydrogenase, alkaline phosphatase, creatine phosphokinase, and C-reactive protein concentrations were measured in blood samples drawn immediately before HD (not fasting).

**"Metabolic syndrome (MS)"**

The diagnosis of MS was made according to the criteria issued the Japanese Society of Internal Medicine [6]. The diagnosis of "MS" was based on the presence of abdominal obesity defined as a waist circumference of 85 cm or more for males and 90 cm or more for females, as well as at least two of the following three modified items:

1. Dyslipidemia (TG [not fasting] > 150 mg/dl and/or HDL-C < 40 mg/dl);
2. High blood pressure before HD (systolic blood pressure > 130 mmHg and/or diastolic blood pressure > 85 mmHg);
3. High plasma glucose (random plasma glucose > 200 mg/dl [7]).

**Statistical Analysis**

The values are expressed as the mean ± SD. The significance of the differences among the groups was calculated using a one-way analysis of variance and an unpaired t-test with the Bonferroni method. P values of < 0.05 were considered to be statistically significant.

**Results**

Although dyslipidemia was observed in only 34 (24.8%) of the 137 maintenance HD patients, only statin therapy and treatment with a single medication was used in 29 of the dyslipidemic patients. Complications of cardiovascular disease were seen in five patients in all groups, two patients in the ACH and PC groups and one patient in the PS group. No acute or chronic adverse effects were noted in the three groups during the follow-up period.

As shown in Table 1, compared to that observed in the PS patients (51.4 ± 9.4 kg), the dry weight levels were significantly greater in the patients receiving ACH (63.0 ± 11.9 kg; P < 0.05). The waist circumference values in the patients receiving the ACH group (90.9 ± 10.5 cm; P < 0.05) were significantly greater than those seen in the patients receiving PS (79.9 ± 10.3 cm). No changes in age, pelvic circumference, waist/pelvic circumference or blood pressure were observed in either statin group during the study period.

As shown in Table 2, the serum creatinine levels in the patients receiving PS (7.5 ± 2.0 mg/dl) were significantly lower among the patients receiving ACH (9.8 ± 2.2 mmHg; P < 0.05) or PC (9.6 ± 1.2 mmHg; P < 0.05) before HD. The blood urea nitrogen levels were significantly higher in the patients receiving ACH (58 ± 17 mg/dl) than in the patients receiving PC (43 ± 13 mg; P < 0.05) before HD. In addition, the serum whole PTH levels were significantly increased in the ACH group (151 ± 102 pg/ml) compared to that seen in the patients being treated with PS (55 ± 32 pg/ml; P < 0.05). Calcinemetics (Cinacalcet hyrochride) was used in three patients in the ACT group (whole PTH: #1 189 pg/ml; #2 22 pg/ml; #3 217 pg/ml), one patient in the PC group (whole PTH: #1 138 pg/ml), and one patients in the PS group (whole PTH: #1 41 pg/ml). No significant differences were noted in the hemoglobin, serum calcium or phosphate levels between the groups.

The serum TG and BMI levels were more significantly increased in the patients treated with ACH (164 ± 75 mg/dl, 24.8 ± 2.9 kg/m\(^2\)) than in the patients being treated with PS (103 ± 36 mg/dl, 21.0 ± 2.9 kg/m\(^2\));

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<th>Group</th>
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<th>ACH</th>
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<tr>
<td>Age (year)</td>
<td>67 ± 10</td>
<td>60 ± 12</td>
<td>59 ± 14</td>
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<tr>
<td>Dry weight (kg)</td>
<td>51.4 ± 9.4</td>
<td>63.0 ± 11.9*</td>
<td>59.1 ± 5.8</td>
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<tr>
<td>Waist circumference (cm)</td>
<td>79.9 ± 10.3</td>
<td>90.9 ± 10.5*</td>
<td>84.6 ± 5.1</td>
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<tr>
<td>Pelvic circumference (cm)</td>
<td>88.2 ± 6</td>
<td>95.3 ± 9.2</td>
<td>91.5 ± 4.0</td>
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<tr>
<td>Waist / Pelvic circumference</td>
<td>0.91 ± 0.06</td>
<td>0.96 ± 0.08</td>
<td>0.92 ± 0.05</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>145 ± 22</td>
<td>149 ± 27</td>
<td>166 ± 24</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>74 ± 11</td>
<td>83 ± 15</td>
<td>84 ± 19</td>
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The data are expressed as the mean ± SD.

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<tr>
<td>Hemoglobin (g/l)</td>
<td>10.2 ± 1.1</td>
<td>10.7 ± 1.6</td>
<td>10.5 ± 0.8</td>
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<tr>
<td>Creatinine (mg/dl)</td>
<td>7.5 ± 2.0</td>
<td>9.8 ± 2.2*</td>
<td>9.6 ± 1.2*</td>
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<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>49 ± 8</td>
<td>58 ± 17</td>
<td>43 ± 13*</td>
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<tr>
<td>Calcium (mg/dl)</td>
<td>9.0 ± 0.6</td>
<td>9.0 ± 0.4</td>
<td>9.4 ± 0.8</td>
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<tr>
<td>Phosphate (mg/dl)</td>
<td>5.1 ± 1.5</td>
<td>5.7 ± 1.2</td>
<td>5.4 ± 1.1</td>
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<tr>
<td>Whole parathyroid hormone (pg/ml)</td>
<td>55 ± 32</td>
<td>151 ± 102*</td>
<td>100 ± 65</td>
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The data are expressed as the mean ± SD.

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The data are expressed as the mean ± SD.

*P < 0.05 compared with the data in the atorvastatin calcium hydrate (ACH) group.

**Table 1:** Physiological data for the ESRD patients treated with statins.

**Table 2:** Renal Data for the ESRD Patients Treated with Statins.

**Citation:** Sanai T, Ono T, Fukumitsu T (2016) Benefits and Adverse Effects of Statins, Atorvastatin Calcium Hydrate, Pitavastatin Calcium, and Pravastatin Sodium, for Dyslipidemia in Patients on Hemodialysis. J Metabolic Synd 5: 202. doi:10.4172/2167-0943.1000202
P < 0.05, Table 3) before HD. The serum LDL-C, HDL-C, non-HDL, postprandial blood glucose, HbA1c, albumin and uric acid levels, were not significantly different between the three groups.

As shown in Table 4, the serum aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, lactate dehydrogenase, alkaline phosphatase, creatine phosphokinase and C-reactive protein concentrations did not differ significantly between the three groups.

The diagnosis of “MS” was made according to the criteria issued by the Japanese Society of Internal Medicine [6] and Japan Diabetes Society [7]. The efficacy of the three statins for treating “MS” (ACH in three patients, PC in two patients and PS in one patient) was not compared. A further study including a smaller number of subjects with “MS” is also needed to confirm the current observations. In the present study, the number of HD patients, including those with MS, was small.

Discussion

In this study, we examined 34 dyslipidemia patients following a routine clinical evaluation of 137 patients with ESRD treated with maintenance HD. In particular, we examined changes in the lipid profiles induced by statins, such as PS, ACH and PC. ACH is a maintenance HD. In particular, we examined changes in the lipid profiles induced by statins, such as PS, ACH and PC. ACH is a maintenance HD.

Table 3: Metabolic Data for the ESRD Patients Treated with Statins.

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<tr>
<td>n</td>
<td>9</td>
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<tr>
<td>LDL (mg/dl)</td>
<td>79 ± 19</td>
<td>79 ± 24</td>
<td>79 ± 18</td>
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<tr>
<td>HDL (mg/dl)</td>
<td>46 ± 18</td>
<td>37 ± 9</td>
<td>43 ± 13</td>
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<tr>
<td>Non-HDL (mg/dl)</td>
<td>108 ± 20</td>
<td>118 ± 31</td>
<td>106 ± 16</td>
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<tr>
<td>TG (mg/dl)</td>
<td>103 ± 36</td>
<td>164 ± 75*</td>
<td>115 ± 39</td>
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<tr>
<td>BMi (kg/m²)</td>
<td>21.0 ± 2.9</td>
<td>24.8 ± 2.9*</td>
<td>23.2 ± 2.7</td>
</tr>
<tr>
<td>PBG (mg/dl)</td>
<td>144 ± 50</td>
<td>114 ± 38</td>
<td>152 ± 82</td>
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<tr>
<td>HbA1c (%)</td>
<td>7.4 ± 1.4 (6)</td>
<td>6.2 ± 0.9 (4)</td>
<td>6.4 ± 1.1 (7)</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>3.8 ± 0.3</td>
<td>3.7 ± 0.4</td>
<td>3.9 ± 0.3</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.8 ± 0.7</td>
<td>6.3 ± 0.5</td>
<td>5.7 ± 0.8</td>
</tr>
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</table>

The data are expressed as the mean ± SD. *P < 0.05 compared with the data in the pravastatin sodium (PS) group. PS: Pravastatin Sodium; ACH: Atorvastatin Calcium Hydrate; PC: Pitavastatin Calcium. LDL: Low-Density Lipoprotein Cholesterol; HDL: High-Density Lipoprotein Cholesterol; TG: Triglyceride; BMI: Body Mass Index = Dry Weight/(Body Weight Immediately After HD) (Kg) / Height X Height (M²); PBG: Postprandial Blood Glucose; Hba1c: Hemoglobin A1c (NGSP).

Today, many statins are clinically available worldwide. Solubility in water or alcohol is related to the tissue selectivity of statins [13]. In Japan, hydrophilic PS has been shown to be superior to lipophilic statins with respect to a preventive Q-wave appearance and reducing cardiovascular events [14].

Yokote et al. [15] reported that the serum HDL-C level shows a significant increase following PC, but not ACH, treatment. In the present study (Table 3), the serum HDL-C levels increased following therapy with PS or PC (mean > 40 mg/dl) and were reduced by ACH treatment (mean < 40 mg/dl).

Lipid-lowering treatment with statins is effective in reducing the risk for cardiovascular disease in early of chronic kidney disease, whereas the benefit of such medication may be limited [16,17] to those an elevated level of LDL-C in patients with chronic kidney disease stage 5D [18] and HD.

Statins are ineffective in the HD patients [19]. ACH may induce obesity-related factors need to be differently influenced. Therefore, it may be other medications that we prevent rather TG rich protein and HDL-C may be limited [16,17] to those elevated level of LDL-C in patients with chronic kidney disease stage 5D [18] and HD.

The serum non-HDL levels are well known to be predictive of a high risk for overall mortality in the general HD associated with dyslipidemia population [1,8] and are closely related to measurements of obesity [9]. Furthermore, the serum TG levels were significantly greater in the patients treated with ACH than in the patients receiving PS group in our study (Table 3). As a result, patients treated with ACH on maintenance HD may have a greater risk of cardiovascular disease in terms of the serum TG levels.

The BMI, dry weight, waist circumference and serum TG levels were significantly greater in the patients receiving ACH than those receiving PS in the current study. However, the clinical and renal data regarding maintenance HD were not significantly different between the three groups, except for the serum whole PTH levels in the ACH group and the serum creatinine levels in the ACH and PC groups. Furthermore, ACH may induce obesity and/or MS, whereas PS or PC may not.

The serum whole PTH levels were significantly increased in the ACH group compared to that seen in the patients being treated with PS (Table 2), whereas the serum calcium, phosphate and alkaline phosphatase levels were not significantly different between the three groups. Rejmark et al. [10] reported the plasma PTH levels to be significantly higher (16%) in statin-treated patients than in control subjects among postmenopausal females. However, in other reports, the plasma levels of PTH and various bone markers did not differ between the simvastatin and control group of postmenopausal women [11]. In addition, statins have no effect on the intact PTH concentration [12]. In this study, the serum PTH levels were differently influenced by the general beneficial effects of statins, including ACH, PS and PC.

In Japan, hydrophilic PS has been shown to be superior to lipophilic statins with respect to a preventive Q-wave appearance and reducing cardiovascular events [14].

The present study was performed in a single arm using a retrospective study and non-controlled design with a small number of patients. However, we firmly believe that the potential benefits of PS and/or PC therapy are important for the improving the rates of cardiovascular morbidity and mortality in HD patients.
Conclusion

The present findings clearly indicate that ACH increases both the BMI and serum TG levels in ESRD patients. In addition, the serum whole PTH levels are expected to provide an option as a marker in ESRD patients treated with ACH. These results suggest that PC may be an ideal statin for the treatment of HD. Future prospective studies with a large number of patients are required to confirm our results.

Acknowledgments

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Disclosure of Interest

The authors declare that no competing financial interests exist (COI).

References


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