Serum ubiquinone concentrations after short- and long-term treatment with HMG-CoA reductase inhibitors

R. Laaksonen¹, J.-P. Ojala², M. J. Tikkanen³, J.-J. Himberg¹

¹ Department of Clinical Pharmacology, University of Helsinki, Finland
² Third Department of Medicine, University of Helsinki, Finland
³ First Department of Medicine, University of Helsinki, Finland

Received: 6 June 1993/Accepted in revised form: 8 December 1993

Abstract. Serum ubiquinone levels were studied during long- and short-term treatment with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors in 17 men with primary non-familial hypercholesterolaemia. The serum ubiquinone levels were determined after the patients had received simvastatin (20-40 mg per day) for 4.7 years, after a 4 week treatment pause and again after they had resumed treatment with lovastatin (20-40 mg per day) for 12 weeks.

During the treatment pause the average serum ubiquinone levels increased by 32%; resumption of treatment caused a reduction of 25%. The changes in the levels of ubiquinone and serum total cholesterol as well as those of ubiquinone and low-density lipoprotein cholesterol were closely parallel.

This suggested that changes in serum ubiquinone reflected changes in cholesterol-containing serum lipoproteins which could serve as carrier vehicles for ubiquinone. After long-term simvastatin treatment and after short-term lovastatin treatment, average serum ubiquinone levels (1.16 and 1.22 mg L⁻¹, respectively) were similar to that observed in a group of apparently healthy middle-aged men (1.16 mg L⁻¹).

Key words: Ubiquinone, Coenzyme Q; lovastatin, simvastatin, long-term treatment

Correspondence to: R. Laaksonen, Department of Clinical Pharmacology, University of Helsinki, Paaskivenkatu 4, SF-00250 Helsinki, Finland

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors or statins, such as lovastatin, simvastatin and pravastatin, constitute a new class of powerful cholesterol-lowering agents. They competitively inhibit the enzyme HMG-CoA reductase which catalyzes the rate-limiting step in cholesterol biosynthesis, i.e. the conversion of HMG-CoA to mevalonate [1]. The statin-induced inhibition of HMG-CoA reductase is thought to decrease the cellular cholesterol content and thus to stimulate the production of low-density lipoprotein (LDL) receptors. This in turn leads to an increased cellular uptake of circulating LDL particles and ultimately to lowered serum total and LDL cholesterol levels [2]. Numerous short-term studies have demonstrated that statins have the potential to lower serum LDL cholesterol levels by 30-40% [3-5]. Moreover, the treatment response has been proven to remain unchanged for several years [6, 7].

Apart from being a key intermediate in cholesterol biosynthesis, mevalonate is a precursor for several nonsterol isoprenoid compounds [8]. It is thus possible that a statin-induced decrease in mevalonate production might cause a reduction in the synthesis not only of cholesterol but also of various nonsterol isoprenoids.

Ubiquinone (also known as coenzyme Q or CoQ) is a nonsterol isoprenoid compound derived from mevalonate. Its major physiological action is to serve as a lipid-soluble electron carrier in the membrane-bound electron transport chains of the mitochondria [9]. Various disease states, such as congestive heart failure and some forms of neuromuscular and periodontal diseases, have been argued to be associated with a deficiency of tissue ubiquinone [10]. Some studies have even suggested that therapeutic benefit could be obtained from the use of ubiquinone for treatment of these disorders [10]. Finally, ubiquinol, the reduced form of ubiquinone, may have a potent antioxidative effect against biological peroxides [11], which might play a protective role against atherogenesis [12]. Thus, the elucidation of the possible effects of statin treatment on ubiquinone metabolism is of clinical importance.

The aim of the present study was to determine whether long-term treatment with a potent HMG-CoA reductase inhibitor resulted in subnormal serum ubiquinone levels. This was prompted by the theory that continuous inhibition of HMG-CoA reductase over the years could cause depletion of ubiquinone stores. Accordingly, serum ubiquinone levels were determined in a group of patients with non-familial hypercholesterolaemia (non-FH) who had received simvastatin for 4.7 years, and compared with levels obtained in healthy middle-aged men. Ubiquinone
levels were also measured after a 4-week treatment pause, and again after resuming treatment with lovastatin to compare the effects of the two inhibitors of HMG-CoA reductase.

**Subjects and methods**

**Subjects**

Patients with statin treatment. Originally the patients had participated in a short-term, double-blind comparison study of simvastatin and gemfibrozil [13], and they continued in a long-term, open-label extension study with simvastatin. In brief, 18 hypercholesterolemic men (pretreatment serum cholesterol 8.3 mmol. l-1) continued with the American Heart Association Phase I diet [14] and received simvastatin at 40 mg per day (n = 14) or 20 mg per day (n = 4). Apart from simvastatin, the patients did not receive any other hypolipidaemic medication. Except for one subject who was lost from follow-up, all patients completed the 4.7-year study; the clinical characteristics of these 17 patients at the end of the follow-up are given in Table 1.

Normal subjects. Fifteen apparently healthy men with total cholesterol level below 6.0 mmol. l-1 were selected as a normal group. They were aged 32-51 years and had no medications or signs of disease. This group was assumed to represent healthy, middle-aged men, but was not designed as a group of matched controls.

**Study design**

After completion of the 4.7-year follow-up study, simvastatin therapy was discontinued in all patients for 4 weeks. After this, 16 of the patients were switched to lovastatin treatment starting with 20 mg nightly. After 6 weeks the dose of lovastatin was increased to 40 mg nightly in six patients. Thus at 12 weeks of lovastatin treatment, 10 patients received lovastatin 20 mg and six patients 40 mg nightly. No other changes in medication or in dietary therapy occurred after discontinuation of simvastatin therapy.

**Laboratory methods**

The fasting blood samples for lipid, lipoprotein and ubiquinone determinations were collected at the end of the 4.7-year follow-up, after the 4-week treatment pause, and 6 and 12 weeks after resuming treatment with lovastatin. The same analyses were carried out in the group of apparently healthy middle-aged men.

**Lipid and lipoprotein analyses.** The concentrations of cholesterol in whole serum and in the high-density lipoprotein (HDL) fraction, as well as serum triglycerides were determined using commercial kits manufactured by Boehringer-Mannheim Diagnostica (Mannheim, Germany). The HDL fraction was obtained by the Mg2+/dextran sulphate precipitation method [15]. LDL cholesterol was calculated using the Friedewald equation [16].

**Ubiquinone.** The ubiquinone determinations were done according to Okamoto et al. [17] by high-performance liquid chromatography (HPLC) with some modifications. The samples were extracted with n-propanol, purified on a C-18 column, and chromatographed as quinones using coenzyme Q9 as an internal standard. The lowest level of detection for plasma samples was 0.1 mg. l-1 and the coefficients of variation (CV) were respectively 7% and 11% for within-day and day-to-day variations for all measured plasma levels.

**Statistical analyses**

Statistical analyses were carried out utilizing SPSS/PC+ and Medstat software and results are expressed as mean with 95% confidence intervals. Wilcoxon's paired test was used for evaluation of the significances of differences. Spearman's correlation coefficients were calculated to assess the associations between total cholesterol and ubiquinone levels and between LDL cholesterol and ubiquinone levels.

**Table 1. Clinical characteristics of statin-treated patients at the end of follow-up (n = 17)**

| Mean age (years) | 57 (38-65) |
| Mean BMI (kg · m-2) | 26 (22-31) |
| Mean duration of statin treatment (years) | 4.7 |
| Number of patients with other drugs | 27 |
| Number of patients with CHD | 14 |

Normal subjects (n = 15): mean age 44 years (32-51), mean BMI 26 kg. m-2 (19-43) BMI, Body mass index; CHD, coronary heart disease

**Table 2. Lipid and lipoprotein data in the statin-treated group and in the control group**

<table>
<thead>
<tr>
<th>Patients with statin treatment</th>
<th>Normal subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>Simvastatin 4.7 years 35 mg; n = 17</td>
</tr>
<tr>
<td>TC (mmol. l-1)</td>
<td>8.3 (7.9-8.8)</td>
</tr>
<tr>
<td>LDL-C (mmol. l-1)</td>
<td>6.2 (5.8-6.7)</td>
</tr>
<tr>
<td>HDL-C (mmol. l-1)</td>
<td>1.14 (1.02-1.25)</td>
</tr>
<tr>
<td>TG (mmol. l-1)</td>
<td>2.11 (1.52-2.69)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results are mean with 95% confidence interval (CI)

TC, Serum total cholesterol; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; TG, triglycerides

Significance of difference from preceding level: * P < 0.05; ** P < 0.01; *** P < 0.001 (Wilcoxon's paired test)

*P mean daily dose