Plasma coenzyme Q (Ubiquinone) concentrations in patients treated with simvastatin

G F Watts, C Castelluccio, C Rice-Evans, N A Taub, H Baum, P J Quinn

Abstract
Plasma coenzyme Q (CoQ) was measured in 20 hyperlipidaemic patients treated with diet and simvastatin (an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase); 22 hyperlipidaemic patients treated with diet with alone; and 20 normal controls. Patients treated with simvastatin had a significantly lower plasma CoQ and CoQ:cholesterol ratio than either patients receiving diet alone or normal controls. Use of simvastatin was inversely and independently correlated with both CoQ (p < 0.0001) and CoQ : cholesterol ratio (p < 0.01). There was a significant inverse association between CoQ and dose of simvastatin (p < 0.001).

It is concluded that simvastatin may lower the plasma CoQ concentration and this may be greater than the reduction in cholesterol. The possible adverse effect of simvastatin on the metabolism of CoQ may be clinically important and requires further study.


Inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (or statins) are widely used to treat hypercholesterolaemia. They inhibit conversion of HMG-CoA to mevalonic acid, the second step in cholesterol biosynthesis, and lower plasma cholesterol by upregulation of low density lipoprotein (LDL) receptors. Statins may also reduce formation of byproducts of the cholesterol biosynthetic pathway, but this is not widely recognised. One important byproduct is coenzyme Q (CoQ, ubiquinone) which has a pivotal role in mitochondrial electron transport and antioxidant activity; deficiency may be clinically relevant. Although data from animals suggest that statins may decrease both plasma and tissue concentrations of CoQ, whether this occurs in humans is not certain.

Simvastatin is the most commonly used statin in the United Kingdom and we have therefore carried out an observational study of patients attending our lipid clinic to examine its possible effect on plasma CoQ concentrations.

Methods
Three groups of subjects were studied: (A) 20 patients (12 men, eight women, aged 55 (SD 8-9) years; five smokers, five with hypertension, and 11 with coronary heart disease) treated with simvastatin and a fat modified diet; (B) 22 patients (nine men, 13 women, aged 53-7 (11-4) years; five smokers, eight with hypertension, and five with coronary heart disease) treated with a fat modified diet alone; (C) 20 healthy, control subjects (10 men, 10 women, aged 48-2 (9-5) years; two smokers) receiving an unrestricted diet. In group A, 14 patients had type IIa hyperlipidaemia (four with familial hypercholesterolaemia) and six type IIb; median dose of simvastatin was 20 mg at night (range 10–80 mg), with mean duration of treatment 15 ± 8 months. In group B, 18 patients had type IIa hyperlipidaemia (two with familial hypercholesterolaemia) and four type IIb. Patients were selected consecutively from attenders at our lipid clinic. Those receiving anti-lipase medication besides simvastatin or with secondary hyperlipidaemia were excluded. Adherence to diet was confirmed from dietetic records, and exercise patterns were similar for groups A and B. Normal subjects were volunteer university staff in excellent health.

Venous blood was collected into tubes containing Na2 EDTA (1 mg/ml), with minimal stasis and with subjects having fasted (12 hours) and in the semi-recumbent position. Cholesterol and triglyceride values were measured enzymatically and high density lipoprotein (HDL) cholesterol after precipitation of apoprotein B with dextran-manganese. LDL cholesterol was calculated by Friedewald formula, except in six patients with triglycerides of > 4-5 mmol/l. Cholesterol was estimated in the d = 1-019–1-063 kg/l fraction after preparative ultracentrifugation in these patients. Coenzyme Q, extracted from plasma as described by Grossi et al, was quantified by reverse phase high power liquid chromatography using a Hichrom C18(0-46 x 30 cm) column and a mobile phase of ethanol/water (2%) with ultraviolet detection at 275 nm. This method had a sensitivity of 0-06 μmol/l and an imprecision (CV) of less than 6%.

Data were compared using an unpaired t test at the 5% level. Plasma CoQ : cholesterol and CoQ : LDL cholesterol ratios were calculated to assess the independent effects of simvastatin on cholesterol and CoQ metabolism. Associations between CoQ (or its ratios) and other variables were examined by general linear modelling.
Plasma lipids, lipoproteins, and coenzyme Q in hypercholesterolaemic patients and controls

<table>
<thead>
<tr>
<th>Group</th>
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<th>Simvastatin</th>
<th>A vs B</th>
<th>Controls</th>
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**Results**

The table shows the plasma lipid, lipoprotein, and CoQ concentrations in the three groups of subjects studied. Group A had significantly lower plasma cholesterol, LDL cholesterol, and CoQ than group B, the difference in CoQ remaining significant after correcting CoQ for cholesterol or LDL cholesterol. There were no significant differences in plasma cholesterol or LDL cholesterol between groups A and C, but group A had significantly higher triglyceride, lower CoQ, and lower CoQ : cholesterol or CoQ : LDL cholesterol ratios. CoQ was significantly higher in group B than in group C (p < 0.05), but this was associated with differences in cholesterol or LDL cholesterol. General linear modelling of patient data showed that plasma CoQ was independently related to age (estimated coefficient 0.01 a year, SE 0.04, p < 0.05) and to use of simvastatin (estimated coefficient −0.48, SE 0.09, p < 0.0001); there were no significant associations with sex, smoking, history of hypertension or coronary heart disease and medication besides simvastatin. Similar analysis showed that the CoQ : cholesterol and CoQ : LDL cholesterol ratios were significantly associated only with use of simvastatin (p < 0.01). There was a significant inverse correlation between plasma CoQ (or its ratios) and the dose of simvastatin (estimated coefficient −0.01/mg, SE 0.002, p < 0.0001), after adjusting for other variables, including body weight. This result also obtained in the simvastatin group alone. Duration of treatment with simvastatin was not, however, significantly correlated with plasma CoQ.

**Discussion**

These preliminary findings suggest that simvastatin may adversely affect the metabolism of CoQ in spite of its well-recognised cholesterol lowering effect. There is dispute, however, as to whether statins lower plasma CoQ independent of reduction in plasma cholesterol. Because these drugs only partially inhibit HMG-CoA reductase, biologically important amounts of mevalonate may be available for synthesis of CoQ. Consistent with this hypothesis are studies in familial hypercholesterolaemia, but these were uncontrolled, of small sample size, or of short duration. By contrast, Folkers et al reported a substantial reduction of plasma CoQ and associated cardiac dysfunction with use of lovastatin, but they referred to patients with cardiomyopathy. The same group also found that in rats lovastatin lowered both plasma and tissue CoQ.

Elberger et al showed that compared with a statin reduction in plasma cholesterol, cholesterylamine did not change the plasma concentrations of CoQ or dolichol, suggesting that our findings may be specific to the HMG-CoA reductase class of lipid lowering drugs. Preliminary data also show that fibrates do not lower plasma CoQ. Although the mechanism whereby simvastatin reduces plasma CoQ is compatible with inhibition of HMG-CoA reductase, it might also inhibit incorporation of tyrosine into ubiquinone. This is compatible with the divergent responses of LDL cholesterol and CoQ. LDL cholesterol and CoQ may also be differentially influenced by LDL receptor activity, thyroid function, exercise and less so by diet, but these factors were controlled for in our study design.

Our study was limited by its observational design, and by lack of pretreatment concentration of CoQ in the simvastatin group. We were, however, able to show an inverse dose-response correlation between simvastatin and plasma CoQ, simvastatin being associated with lower than normal concentrations of CoQ even after correcting for differences in plasma cholesterol. That patients receiving simvastatin had significantly lower CoQ concentrations than patients treated by diet alone excludes a confounding effect of diet, given that there was no significant difference in CoQ between the diet and control groups. Moreover, demographic characteristics were similar among the groups, and patients were representative of those usually attending a lipid clinic. Proof for a causal relation between use of simvastatin and low plasma CoQ ultimately requires a randomised controlled trial. This should ideally focus on both plasma and tissue CoQ oxidizability of LDL, and measures of atherosclerosis.

Coenzyme Q is essential for mitochondrial function and antioxidant activity. As plasma and tissue concentrations of CoQ are in equilibrium, we suggest that a reduction in plasma CoQ may underpin some of the severe side-effects of statins, but this requires confirmation. Moreover, given the important role of oxidative mechanisms in atherosclerosis, a reduction in CoQ may also compromise the course of coronary atherosclerosis despite optimal concentrations of LDL cholesterol. Pending further studies, we recommend that consideration be given to measuring plasma CoQ in patients receiving statins and particularly in those with clinically important cardiac disease. Confirmed deficiency may be corrected by dietary supplementation with CoQ.

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Septic arthritis and unpasteurised milk

P Campbell, S Dealler, J O Lawton

Abstract

Green-top, or unpasteurised, milk is an increasing source of illness. A case of a previously unreported cause of septic arthritis of the hip joint, secondary to the ingestion of raw milk is reported.

(J Clin Pathol 1993;46:1057–1058)

Case report

A 57 year old woman was admitted to hospital with a 10 week history of pain around the left hip. There had been no precipitating injury or previous similar problems. An x ray picture (fig 1) at the onset of the symptoms had shown moderate degenerative changes only. The pain had persisted and there had been no other associated symptoms. There was no clinically relevant medical history.

Examination showed that the patient had no fever. The left hip was held in 30° of fixed flexion with severe quadriceps wasting. All hip movements were painful and restricted. The rest of the examination yielded completely normal results. X ray pictures on admission (fig 2) showed obvious destruction of the left hip joint. Initial blood tests showed a raised white cell count and plasma viscosity, but a normal bone biochemistry profile. Chest x ray picture was also normal.

Aspiration of the hip produced a sample of viscid pus, culture of which gave a pure growth of Streptococcus lactis. Acid fast bacilli were neither seen on microscopical examination nor cultured. Other investigations, including blood glucose, rheumatoid factor, and brucellosis titres were normal. An isotope bone scan confirmed increased isotope uptake around the left hip, but no other septic foci. In view of the established joint destruction open drainage of the joint was not performed and the patient was managed conservatively with initially intravenous, and then oral, penicillin, straight skin traction to the left leg, and two hours of lying prone daily.

The pain gradually settled and the patient was mobilised in a hip spica to encourage the development of a painless ankylosis. Antibiotics were continued for six weeks and the spica retained for a total of three months. When reviewed at eight months after discharge, there was some shortening of the left leg secondary to a 30° fixed flexion deformity at the hip, but the patient was walking with one stick, had no rest pain, and only minimal discomfort on activity which was improving.

On further questioning prior to discharge, the patient stated that she came from a farming community and drank exclusively unpasteurised milk.

Discussion

The principles of treatment of bacterial arthritis are drainage of the joint, culture of the organism, antibiotics and articular rest. There are no prospective trials comparing

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Figure 1 X ray picture showing moderate degenerative changes.
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