ORIGINAL CONTRIBUTION

Atorvastatin Decreases the Coenzyme Q_{10} Level in the Blood of Patients at Risk for Cardiovascular Disease and Stroke

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Background: Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are widely used for the treatment of hypercholesterolemia and coronary heart disease and for the prevention of stroke. There have been various adverse effects, most commonly affecting muscle and ranging from myalgia to rhabdomyolysis. These adverse effects may be due to a coenzyme Q_{10} (CoQ_{10}) deficiency because inhibition of cholesterol biosynthesis also inhibits the synthesis of CoQ_{10}.

Objective: To measure CoQ_{10} levels in blood from hypercholesterolemic subjects before and after exposure to atorvastatin calcium, 80 mg/d, for 14 and 30 days.

Design: Prospective blinded study of the effects of short-term exposure to atorvastatin on blood levels of CoQ_{10}.

Setting: Stroke center at an academic tertiary care hospital.

Patients: We examined a cohort of 34 subjects eligible for statin treatment according to National Cholesterol Education Program: Adult Treatment Panel III criteria.

Results: The mean±SD blood concentration of CoQ_{10} was 1.26±0.47 µg/mL at baseline, and decreased to 0.62±0.39 µg/mL after 30 days of atorvastatin therapy ($P<.001$). A significant decrease was already detectable after 14 days of treatment ($P<.001$).

Conclusions: Even brief exposure to atorvastatin causes a marked decrease in blood CoQ_{10} concentration. Widespread inhibition of CoQ_{10} synthesis could explain the most commonly reported adverse effects of statins, especially exercise intolerance, myalgia, and myoglobinuria.

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EVER SINCE THEIR INTRODUCTION in the US Pharmacopoeia at the end of the 1980s, statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) have been widely and successfully used for the treatment of hypercholesterolemia and coronary artery disease and for the prevention of stroke. New evidence suggests that the effect of statins on the vascular system may not be mediated by their lipid-lowering properties, but rather by their anti-inflammatory (antiatherosclerotic) action. These "wonder drugs," however, have also been associated with various adverse effects, most commonly involving muscle and ranging from myalgia to muscle breakdown and myoglobinuria.[1-3] In the case of cerivastatin sodium (Baycol), the adverse effects were so common and severe that the drug was withdrawn from the market.

The logical explanation for the adverse effects of statins is that they inhibit cholesterol synthesis effectively but not selectively, because the biosynthetic pathway of cholesterol is shared by other compounds, including coenzyme Q_{10} (CoQ_{10}; ubiquinone).[1] In humans, CoQ_{10} is not only a vital component of the mitochondrial respiratory chain but also a membrane stabilizer and an excellent oxygen radical scavenger.[4] Thus, a substantial decrease of the CoQ_{10} level induced by statins could explain some of their adverse effects. This hypothesis is especially attractive because a rare, presumably primary, form of CoQ_{10} deficiency causes a mitochondrial encephalomyopathy with recurrent myoglobinuria.[5-7]

Several statins, including lovastatin (Mevacor),[8,9] simvastatin (Zocor),[10,11] and pravastatin sodium (Pravachol),[9,10] do decrease CoQ_{10} levels in the blood of patients and control subjects, although the number of subjects studied and the severity of CoQ_{10} deficiency varied markedly in different reports. Surprisingly, one randomized crossover study[12] of pravastatin and atorvastatin calcium (Lipitor) failed

to find any decrease of blood CoQ_{10} level in healthy volunteers.

We had a unique opportunity to study the short-term effects of atorvastatin, 80 mg/d, on blood CoQ_{10} level in 35 subjects who were eligible for statin treatment according to the criteria of the National Cholesterol Education Program: Adult Treatment Panel (NCEP ATP) III.[13] This study was an add-on to a longitudinal B-mode carotid ultrasonographic imaging study of the effect of a daily dose of atorvastatin on carotid wall elasticity. The aim of this corollary study was to test the hypothesis that short-term exposure to atorvastatin, 80 mg/d for 30 days, might significantly decrease plasma CoQ_{10} levels compared with pretreatment levels. A secondary hypothesis was that this effect might be rapid and already detectable 2 weeks after the initiation of treatment.

METHODS

SUBJECTS

Forty subjects older than 45 years with an elevated low-density lipoprotein cholesterol level, as defined by the NCEP ATP III, were included in a longitudinal B-mode carotid ultrasonographic imaging study aimed at evaluating the possible rapid effect of a single dose of atorvastatin on carotid artery wall elasticity.

To be eligible for atorvastatin treatment according to the NCEP ATP III criteria, the subjects had to have the following features: (1) known coronary heart disease (CHD) or CHD equivalent (peripheral artery disease, abdominal aortic aneurysm, symptomatic carotid artery disease, diabetes mellitus, or multiple risk factors for CHD conferring a 10-year risk factor for coronary artery disease of >20%), (2) 2 or more risk factors for CHD and a low-density lipoprotein cholesterol level of 130 mg/dL or higher (≥3.36 mmol/L), or (3) no risk factors or one risk factor and a low-density lipoprotein cholesterol level higher than 160 mg/dL (>4.14 mmol/L).

The NCEP ATP III–defined risk factors included the following: (1) age for men of 45 years or older and for women, 55 years or older; (2) hypertension, a blood pressure of 140/90 mm Hg or higher, or the need for antihypertensive therapy; (3) a high-density lipoprotein cholesterol level of less than 40 mg/dL (<1.03 mmol/L); (4) cigarette smoking; and (5) family history of premature CHD or CHD in first-degree relatives (men, <55 years; and women, <65 years).

Exclusion criteria included active hepatic or renal dysfunction, connective tissue disease, chronic inflammatory disease, malignancy or history of malignancy, any acute illness, leukocytosis (white blood cell count, $>10\times10^3$/μL), thrombocytosis (platelet count, $>450\times10^3$/μL), anemia (hematocrit, <40%), and corticosteroid therapy. Patients hospitalized for acute coronary syndrome within 6 months of the start of the study were excluded. Women who were nursing and who were or might become pregnant were not eligible. Patients being treated for hyperlipidemia with a statin were excluded.

The prospective study subjects were screened for eligibility based on their risk factor profiles and the NCEP ATP III criteria. The conduct of the study was approved by the Western Institutional Review Board. Informed consent was obtained before enrollment at the baseline visit.

All subjects received oral atorvastatin, 80 mg/d, for 30 days. The study assessments included a fasting blood test, carotid ultrasonography, and the determination of inflammatory markers at baseline (before atorvastatin treatment) and 14 and 30 days thereafter. At the 14- and 30-day visits, subjects were examined for changes in liver enzyme levels, renal function, and any severe and nonsevere described adverse effects. In particular, subjects were monitored for muscle pain or weakness. Commonly reported, but often transient, adverse effects, such as flatulence, constipation, stomach pain, and indigestion, were noted.

PROCEDURES

After a 12-hour fast, blood was drawn by phlebotomy, collected in EDTA-additive tubes, and centrifuged immediately at 4°C at 3000 rpm for 20 minutes. The plasma was removed and stored at −80°C. At the end of the study, all plasma samples available after primary analysis of lipid profiles were used for the CoQ_{10} assay (baseline, 34 subjects; 14 days of atorvastatin therapy, 32 subjects; and 30 days of atorvastatin therapy, 36 subjects).

Coenzyme Q_{10} was extracted from plasma (a 50-μL sample and 950 μL of ice-cold 1-propanol) by vortex mixing in a microcentrifuge tube for 2 minutes; after centrifugation at 14 000 rpm for 10 minutes at 4°C, 30 μL of clear supernatant was injected directly into the high-performance liquid chromatographic system. High-performance liquid chromatographic analyses were performed using a reverse-phase isocratic system, as previously described.[14]

STATISTICAL ANALYSIS

Coenzyme Q_{10} concentrations are expressed as the mean±SD and as interquartile ranges before atorvastatin treatment and 14 and 30 days after the initiation of treatment. An analysis of variance was used to compare CoQ_{10} levels at baseline and at the 2 follow-up visits. Absolute and relative CoQ_{10} changes at 14 and 30 days were compared by a paired *t* test. Relative changes were calculated by dividing percentage differences from baseline by baseline values, multiplied by 100. Differences were 1-tailed and considered statistically significant at $\alpha=.05$. Data for other variables are given as mean±SD.

RESULTS

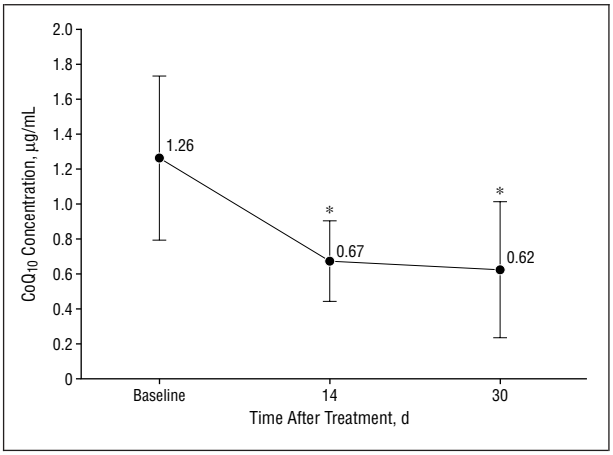
We studied 34 subjects (18 men and 16 women) who had plasma CoQ_{10} levels measured at baseline and 1 month after treatment with atorvastatin. Their age was 70±7 years. They included Caribbean Hispanic subjects (22 [64%]), African American subjects (8 [24%]), and white subjects (4 [12%]).

The concentration of CoQ_{10} at baseline in these 34 individuals was 1.26±0.47 μg/mL (range, 0.66-3.04 μg/mL) (interquartile ranges: quartile 1, 0.66-1.00 μg/mL; quartile 2, 1.01-1.26 μg/mL; quartile 3, 1.27-1.44 μg/mL; and quartile 4, 1.45-1.84 μg/mL), well in line with our own values in healthy individuals (0.84±0.29 μg/mL) and with values in the literature. These values were not significantly different by age (<70 vs ≥70 years; $P=.46$, *t* test), sex ($P=.35$, *t* test), or race ($P=.74$, analysis of variance).

After 30 days of atorvastatin therapy, the plasma CoQ_{10} concentration decreased significantly from baseline (CoQ_{10} level at 30 days, 0.62±0.39 μg/mL; absolute reduction, 0.66 μg/mL; and relative reduction, 52%; $P<.001$). A significant ($P<.001$) decrease was also detected after 14 days of treatment, when the plasma CoQ_{10} level in 32 subjects had decreased by 49% (**Figure**). The decreases between baseline and day 30 in total cholesterol (220±43 vs 131±31 mg/dL [5.7±1.1 vs 3.4±0.8

mmol/L]; $P<.001$), low-density lipoprotein cholesterol (143±39 vs 70±27 mg/dL [3.7±1.0 vs 1.8±0.7 mmol/L]; $P<.001$), and triglycerides (142±71 vs 97±35 mg/dL [1.6±0.8 vs 1.1±0.4 mmol/L]; $P<.004$] were similar (using the paired *t* test).

The intraindividual CoQ_{10} change was 0.64±0.28 µg/mL (relative reduction, 49%; $P<.001$) after 30 days of atorvastatin therapy, and 0.67±0.23 µg/mL (relative reduction, 45%; $P<.001$) after 14 days of treatment (Figure). In all subjects and at both follow-up visits, plasma concentrations of CoQ_{10} were significantly ($P<.001$) lower than at baseline. In 2 subjects, CoQ_{10} concentrations were higher on day 30 than on day 14, but still lower than at baseline. One of these 2 subjects stopped taking atorvastatin after 10 days, and the other was noncompliant, taking the pills only occasionally.



Mean±SD plasma coenzyme Q_{10} (CoQ_{10}) concentrations at baseline and at 14 and 30 days after atorvastatin calcium therapy. The asterisk indicates that the value is significantly different ($P<.001$) from baseline.

COMMENT

Few drugs are as widely used as the statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, that effectively decrease blood levels of cholesterol and protect against various cardiovascular diseases related to atherogenesis. Similarly, few drugs have generated as much controversy as the statins[2]: adverse effects, predominantly affecting skeletal muscle,[3,15] have been widespread and severe enough to force one pharmaceutical company to withdraw cerivastatin from the market. However, statins are still widely used and their safety is still debated. The common mechanism of action of these drugs, inhibition of cholesterol metabolism at the level of mevalonic acid, has the unintended consequence of impairing the synthesis of other compounds that share mevalonate as a precursor, such as dolichols and CoQ_{10} (ubiquinone). In our well-controlled longitudinal study, atorvastatin caused a rapid and substantial decrease of plasma CoQ_{10} concentrations, which was evident 14 days after the initiation of therapy and was even more marked after 30 days of therapy.

Impaired synthesis of CoQ_{10} could well explain the variety of adverse effects reported because of the central role of this compound in energy generation through the mitochondrial respiratory chain and because of its antioxidant properties.[4] Indirect support for a pathogenic role of CoQ_{10} deficiency comes from data from patients with idiopathic—presumably primary—CoQ_{10} deficiency. These patients have a mitochondrial encephalomyopathy, most commonly presenting as an autosomal recessive spinocerebellar atrophy syndrome.[16,17] A rarer myopathic variant combines central nervous system signs (ataxia, epilepsy, and mental retardation) with a mitochondrial myopathy dominated by recurrent rhabdomyolysis and myoglobinuria (which is, perhaps not coincidentally, one of the most severe adverse effects of statin treatment).[5-7]

It is, therefore, not surprising that, starting with Folkers et al,[18] several groups have studied the effects of statins on the blood concentration of CoQ_{10} in humans, in patients with hypercholesterolemia and in healthy subjects. It is somewhat difficult to compare results because different studies used different statins, different dosages, and long- or short-term exposures. In addition, some studies were conducted on few or even single individuals, and others on larger series. A double-blind placebo-controlled study[10] of healthy volunteers treated for 1 month with either pravastatin, 20 mg/d (n=10), or simvastatin, 20 mg/d (n=10), for 4 weeks showed similar decreases (50% and 54%, respectively) of blood CoQ_{10} levels, whereas 10 individuals receiving placebo showed no change. In another large study,[9] 45 hypercholesterolemic patients were randomized in a double-blind trial: one group received increasing doses of pravastatin sodium (20, 40, and 80 mg/d) and a second group received increasing doses of lovastatin (10, 20, and 40 mg/d) for a total of 18 weeks. In both groups, there was a gradual decrease of blood CoQ_{10} level: after 18 weeks, the CoQ_{10} level was 80% of baseline with pravastatin and 71% of baseline with lovastatin.

The only study[12] with negative results involved 12 healthy subjects: 6 received pravastatin sodium, 20 mg/d, for 4 weeks and 6 received atorvastatin calcium, 10 mg/d, for 4 weeks. After a washout period, each group received the alternate drug for another 4 weeks. No change in blood CoQ_{10} level was found at the end of each treatment. This study is noteworthy because—like ours—it used atorvastatin, although the dose was much lower than that used by us and the number of subjects was much smaller.

We took advantage of the availability of blood samples from a large cohort of hypercholesterolemic patients in whom we studied the short-term (2- and 4-week) effects of atorvastatin calcium, 40 mg/d, on carotid artery elasticity by B-mode ultrasonography. The results on carotid artery elasticity will be reported elsewhere. This was a large and uniform population of patients from whom samples of plasma were obtained at baseline and after 2 and 4 weeks of therapy. All samples were kept frozen until the CoQ_{10} assay to minimize methodological variations. Baseline CoQ_{10} concentrations corresponded to accepted normative values, from our own experience and from the literature, and were relatively uniform (Figure). There was a highly significant and marked (about 50%) decrease of the CoQ_{10} concentration after 2 weeks of atorvastatin administration, which was essentially unchanged after 4 weeks of treatment. To our knowledge,

this is the first unequivocal demonstration that atorvastatin—like pravastatin and simvastatin[10]—also reduces blood levels of CoQ_{10}, and to about the same extent.

Our patients did not report severe adverse effects during 30 days of exposure to atorvastatin. In particular, there were no complaints of myalgia or weakness. Only one subject experienced weakness and tingling in the legs, which disappeared 2 days after reducing the dose of atorvastatin calcium to 40 mg/d (the plasma CoQ_{10} level was 0.84 µg/mL at baseline, 0.38 µg/mL on day 14, and 0.34 µg/mL on day 30). The most common adverse effects were flatulence and constipation, which usually resolved within days.

Our study does not address the question of whether tissue levels of CoQ_{10} were also decreased by atorvastatin. One previous study[11] of healthy volunteers treated with simvastatin, 20 mg/d, for 4 weeks had shown a 30% decrease of blood CoQ_{10} level, contrasting with a paradoxical increase of muscle CoQ_{10} level. Despite this limitation, our findings raise the possibility of a widespread inhibition of CoQ_{10} synthesis in patients treated with atorvastatin. Given the many patients exposed to relatively high doses of this drug and the persistent occurrence of adverse effects related to statins, it may be reasonable to add CoQ_{10} in patients receiving long-term treatment with statins in general, and atorvastatin in particular. This recommendation is strengthened by the general experience that oral CoQ_{10}—even in high doses—is well tolerated by patients.[16,17,19-23]

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