Atorvastatin Decreases the Coenzyme Q₁₀ 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 Q₁₀ (CoQ₁₀) deficiency because inhibition of cholesterol biosynthesis also inhibits the synthesis of CoQ₁₀.

Objective: To measure CoQ₁₀ 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 CoQ₁₀.

Setting: Stroke center at an academic tertiary care hospital.

Results: The mean±SD blood concentration of CoQ₁₀ 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 CoQ₁₀ concentration. Widespread inhibition of CoQ₁₀ synthesis could explain the most commonly reported adverse effects of statins, especially exercise intolerance, myalgia, and myoglobinuria.

Arch Neurol. 2004;61:889-892

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 In humans, CoQ₁₀ is not only a vital component of the mitochondrial respiratory chain but also a membrane stabilizer and an excellent oxygen radical scavenger.² Thus, a substantial decrease of the CoQ₁₀ level induced by statins could explain some of their adverse effects. This hypothesis is especially attractive because a rare, presumably primary, form of CoQ₁₀ deficiency causes a mitochondrial encephalomyopathy with recurrent myoglobinuria.³⁻⁷

Several statins, including lovastatin (Mevacor),⁸⁻⁹ simvastatin (Zocor),¹⁰⁻¹¹ and pravastatin sodium (Pravachol),⁹⁻¹⁰ do decrease CoQ₁₀ levels in the blood of patients and control subjects, although the number of subjects studied and the severity of CoQ₁₀ deficiency varied markedly in different reports. Surprisingly, one randomized crossover study¹² of pravastatin and atorvastatin calcium (Lipitor) failed...
to find any decrease of blood CoQ10 level in healthy volunteers.

We had a unique opportunity to study the short-term effects of atorvastatin, 80 mg/d, on blood CoQ10 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. This study was an add-on to a longitudinal B-mode carotid ultrasonographic imaging study aimed at evaluating the possible rapid effect of a single 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 CoQ10 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 × 10⁹/µL), thrombocytosis (platelet count, >450 × 10⁹/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 CoQ10 assay (baseline, 34 subjects; 14 days of atorvastatin therapy, 32 subjects; and 30 days of atorvastatin therapy, 36 subjects).

Coenzyme Q₁₀ 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.

STATISTICAL ANALYSIS

Coenzyme Q₁₀ 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 CoQ₁₀ levels at baseline and at the 2 follow-up visits. Absolute and relative CoQ₁₀ 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 α = .05. Data for other variables are given as mean±SD.

RESULTS

We studied 34 subjects (18 men and 16 women) who had plasma CoQ₁₀ 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 CoQ₁₀ 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 CoQ₁₀ concentration decreased significantly from baseline (CoQ₁₀ 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 CoQ₁₀ 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]...
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 atherosclerosis. Similarly, few drugs have generated as much controversy as the statins: adverse effects, predominantly affecting skeletal muscle, 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 CoQ10 (ubiquinone). In our well-controlled longitudinal study, atorvastatin caused a rapid and substantial decrease of blood CoQ10 level: after 18 weeks, the CoQ10 level was found at the end of each treatment. This impairment of CoQ10 synthesis could well explain the marked decrease of blood CoQ10 level: after 18 weeks, the CoQ10 level was 80% of baseline with pravastatin and 71% of baseline with lovastatin.

Mean ± SD plasma coenzyme Q10 (CoQ10) 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**

Studies were conducted on few or even single individuals, and others on larger series. A double-blind placebo-controlled study 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 CoQ10 levels, whereas 10 individuals receiving placebo showed no change. In another large study, 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 CoQ10 level: after 18 weeks, the CoQ10 level was 80% of baseline with pravastatin and 71% of baseline with lovastatin.

The only study 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 CoQ10 level was found at the end of each treatment. This study is noteworthy because—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 CoQ10 assay to minimize methodological variations. Baseline CoQ10 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 CoQ10 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\textsuperscript{10}—also reduces blood levels of CoQ\textsubscript{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\textsubscript{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\textsubscript{10} were also decreased by atorvastatin. One previous study\textsuperscript{11} of healthy volunteers treated with simvastatin, 20 mg/d, for 4 weeks had shown a 30% decrease of blood CoQ\textsubscript{10} level, contrasting with a paradoxical increase of muscle CoQ\textsubscript{10} level. Despite this limitation, our findings raise the possibility of a widespread inhibition of CoQ\textsubscript{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\textsubscript{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\textsubscript{10}—even in high doses—is well tolerated by patients.\textsuperscript{10,17,19-23}

\textbf{Accepted for publication January 27, 2004.}

\textbf{Author contributions:} Study concept and design (Drs Rundek, Naini, Sacco, and DiMauro); acquisition of data (Drs Rundek and Sacco and Ms Coates); analysis and interpretation of data (Drs Rundek, Naini, Sacco, and DiMauro and Ms Coates); drafting of the manuscript (Drs Rundek, Naini, and DiMauro); critical revision of the manuscript for important intellectual content (Drs Rundek, Naini, Sacco, and DiMauro and Ms Coates); statistical expertise (Dr Rundek and Ms Coates); obtained funding (Dr Rundek); administrative, technical, and material support (Ms Coates); study supervision (Drs Rundek, Naini, Sacco, and DiMauro).

This study was supported by an investigator-initiated grant from Pfizer Inc, New York, NY; the Hazel K. Goddess Fund (Dr Rundek); and a grant from the Muscular Dystrophy Association, Tucson, Ariz (Dr DiMauro).

We thank Luisa Godoy, BS, for her dedication to the patients in the study; and Annette Szumski, MS, for her assistance with data management and statistical analysis.

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