Effect of Simvastatin and Atorvastatin on Coenzyme Q10

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Citation

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Abstract

Background: Coenzyme Q10 (CoQ10) is an antioxidant and plays an important role in the synthesis of adenosine triphosphate. Studies suggest that 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors reduce CoQ10 levels.

Aims: To determine the effect of 2 different HMG-CoA reductase inhibitors, Simvastatin and atorvastatin, on CoQ10 levels in a randomized crossover fashion.

Methods: 30 healthy volunteers received either 20 mg Simvastatin (S) or 10 mg atorvastatin (A) for 4 weeks in a randomized crossover fashion. There was a 4- to 8-week washout period between the 2 phases. CoQ10 levels and a lipid profile were estimated as per publish procedure.

Results: There was no difference in CoQ10 levels from baseline to post-drug therapy for either S or A. There was a significant difference in Lipid profile levels from baseline to post-drug therapy for both S and A There was no significant correlation between LDL and CoQ10.

Conclusions: S and A did not decrease CoQ10 levels. These findings suggest that HMG-CoA reductase inhibitors do not significantly decrease the synthesis of circulating CoQ10 in healthy subjects. Routine supplementation of CoQ10 may not be necessary when HMG-CoA reductase inhibitor therapy is administered.

INTRODUCTION

Coenzyme Q 10 (CoQ10), a lipophilic compound, is naturally found throughout the body including the heart, liver, and skeletal muscle ([1,2]). CoQ10 acts in the body as an antioxidant and may have membrane-stabilizing properties ([1,3,4,5]). In addition, CoQ10 is an important factor for cellular mitochondrial respiration. In other words, CoQ10 is essential for energy production (cellular bioenergetics) including in the heart. The cellular effects of CoQl0 may be especially important in patients with cardiac disease, specifically coronary artery disease and congestive heart failure. The major use of Coenzyme Q10 would be in the case of congestive heart failure, where it is particularly effective. Its importance to the human heart is illustrated by the fact that the heart may cease to function as coenzyme Q10 levels fall by 75%.

Hyperlipidemia needs to be aggressively treated, especially in patients with a history of cardiac disease, including heart failure. The most important classes of drugs for treating hyperlipidemia is the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins). However, recent studies have shown that HMG-CoA reductase inhibitors may reduce plasma CoQl0 levels ([6,7,8]) by competitively inhibiting the conversion of HMG-CoA to mevalonate, a precursor for CoQ10. Simvastatin was decided on the basis of previous studies suggesting that this drug has limited effects in reducing CoQ10 levels and is less lipophilic than atorvastatin. Atorvastatin was chosen on the basis of its lipophilicity and because it is the most potent HMG-CoA reductase that theoretically may have the greatest effect on reducing mevalonate and CoQ10 among the reductase inhibitors.

Therefore the purpose of this study was to determine the effect of 2 different HMG-CoA reductase inhibitors, simvastatin (S) and atorvastatin (A), on CoQ10 levels in a randomized crossover fashion.

MATERIAL AND METHODS

PATIENTS AND STUDY DESIGN

A total of 30 healthy subjects completed an open-label randomized crossover trial evaluating the effect of simvastatin and atorvastatin on CoQ10 plasma levels. The institutional ethics committee gave approval and informed consent was obtained from every patient. Inclusion criteria included the following: age >18 years and normolipidemic, defined as low-density lipoprotein (LDL) levels <160 mg/dL, total cholesterol (TC) levels <200 mg/dL, high-density lipoprotein (HDL) levels >35 mg/dL, and triglycerides (TG) <160 mg/dL. Individuals taking scheduled medications concurrently, those with significant medical histories, as well as smokers and pregnant females were excluded from the study.

Subjects were admitted to the General Clinical ward, and after physical examination and baseline laboratory measurements were obtained patients were randomized into one of 2 groups: simvastatin 20 mg daily for a 4-week period (S) or atorvastatin 10 mg daily for a 4-week period (A). After the 4-week treatment period there was a 4- to 8-week washout period to minimize any carryover effects and to ensure that lipid levels were back to baseline values. After the washout period, subjects received the alternate drug for another 4 weeks. Laboratory measurements of CoQ10, lipids, and LFTs were taken before and after each treatment including the washout phase; levels before the start of the first phase and at the end of washout were considered to be baseline.

Patients also were required to keep a dietary journal. At baseline, an in-person 24-hour dietary recall was conducted and reviewed by a registered dietitian.

COQ10 ASSAY

For the CoQl0 analysis, 7 mL of whole blood was collected from a forearm vein. Whole blood concentrations of CoQ10 were determined by high-pressure liquid chromatography (HPLC) by a modification of the method of Johansen K ($_{13}$) in which coenzyme Q7 was substituted for coenzyme Q11 as the internal standard. The limit of detection was 0.1 to 15 mg/mL.

STATISTICAL ANALYSIS

The data were analyzed by a paired t test within and between groups. In addition, the Pearson correlation was used to determine whether a relationship existed between CoQ10 and lipid parameters (LDL, TC, HDL, TG). A “P” value <0.05 was considered as statistical significant. The reported data are represented as the Mean (SD).

RESULTS

There were a total of 30 patients completing the study, 20 male and 10 female. The subjects ranged in age from 25 to 45 years old (mean 31.2 ± 9.3 years), and all were within 30% of their ideal body weights.

The results for CoQ10 and lipid profile from baseline to post-treatment for each treatment phase are shown in Tables 1 and 2. For both groups there were significant decreases in TC and LDL as expected. Simvastatin demonstrated a significant increase in HDL levels, whereas atorvastatin did not. For both treatment phases there was no significant change in CoQ10 concentrations from baseline to post-therapy. In fact, the concentration at baseline was nearly identical to the concentration after therapy.

Figure 1

Table 1: CoQ10 and lipid profile before and after simvastatin therapy

Variable	Baseline	After Treatment
Coenzyme Q10 (mg/ml)	0.7 (0.2)	0.64 (0.21)
TC (mg/dl)	175 (31)	135 (23) *
TG (mg/dl)	95 (21)	70 (25)*
HDL - Cholesterol (mg/dl)	47 (9)	55 (11)*
LDL- Cholesterol (mg/dl)	95 (24)	68 (19)*

Values Expressed as Mean (SD)
P<0.05 as compared to Base line
TC – Total cholesterol
TG – Triglyceride
HDL - Cholesterol – High Density Lipoprotein – Cholesterol
LDL - Cholesterol – Low Density Lipoprotein - Cholesterol

Figure 2

Table 2: CoQ10 and lipid profile before and after atorvastatin therapy

Variable	Baseline	After Treatment
Coenzyme Q10 (mg/ml)	0.65 (0.19)	0.60 (0.15)
TC (mg/dl)	174 (30)	130 (20)*
TG (mg/dl)	90 (11)	65 (16)*
HDL (mg/dl)	50 (9)	55 (10)
LDL (mg/dl)	111 (28)	70 (12)*

Values Expressed as Mean (SD)
* P<0.05 as compared to Base line
** p<0.05 as compared to Base line
TC – Total cholesterol
TG – Triglyceride
HDL - Cholesterol – High Density Lipoprotein – Cholesterol
LDL - Cholesterol – Low Density Lipoprotein - Cholesterol

There were no statistical differences in the baseline values between the 2 groups. When the mean change in CoQ10 and lipid concentrations was compared between the 2 treatment groups, a significantly greater decrease in LDL concentrations was observed in the atorvastatin group (Table 3). No significant difference was seen for CoQ10.

Figure 3

Table 3: Mean change in CoQ10 and lipid profile before and after therapy for simvastatin and atorvastatin

Variable	Simvastatin	Atorvastatin	P value
Coenzyme Q10 (mg/ml)	0.06 ± 0.22	- 0.05 ± 0.14	0.40
TC (mg/dl)	- 40 ± 10	- 44 ± 14	0.44
TG (mg/dl)	- 25 ± 14	- 25 ± 0.18	0.40
HDL (mg/dl)	8 ± 5	5 ± 11	0.42
LDL (mg/dl)	- 27 ± 15	- 41 ± 19	0.01

The correlation between CoQl0 and lipid variables (TC, LDL, HDL, and TG) was also evaluated. There was no significant correlation between CoQ10 and TC, LDL, or TG, demonstrating that as these lipid concentrations are decreased CoQ10 decreases. There was also no correlation between HDL concentrations and CoQ10.

DISCUSSION

The results of this study demonstrated that there was no difference between simvastatin and atorvastatin in decreasing CoQl0 concentrations in healthy subjects. In fact, the data suggest that these drugs had no effect at all in decreasing CoQ10 concentrations after 4 weeks of therapy despite significant decreases in TC and LDL.

The finding that neither HMG-CoA reductase inhibitor reduced CoQ10 concentrations was not expected. Many studies have shown that HMG-CoA reductase inhibitors including simvastatin, lovastatin, and simvastatin significantly reduce CoQ10 concentrations after treatment ([6,7,8]). The majority of studies evaluating CoQ10 has been performed in patients with hypercholesterolemia; however, one study evaluated 2 groups of 5 healthy volunteers and demonstrated a reduction in CoQ10 of up to 40% after drug therapy ([9]). Another study demonstrated that at both a 10-mg and 20-mg dose of simvastatin that significant reduction in CoQl0 and TC occurred ([10]). These findings suggest that our study design was sufficient to allow an HMG-CoA reductase inhibitor to reduce CoQ10 concentrations.

In addition, in support of this study design, there were significant decreases in TC and LDL after 4 weeks of therapy for both drugs in this study. HMG-CoA reductase inhibitors competitively inhibit the enzyme HMG-CoA reductase, which decreases the conversion of HMG-CoA to mevalonate, which is a precursor to cholesterol synthesis ([11]). Mevalonate is also thought to be a precursor for the synthesis of several isoprenoid compounds, including CoQ10 ([12]). Therefore the reduction in TC and LDL as a result of the drug therapy should have ensured a decrease in CoQ10. The decrease in CoQl0 after statin therapy is due to a reduction in transport molecules and not in the synthesis of CoQl0. The reason why CoQ10 synthesis may not be affected by HMG-CoA reductase inhibition is not known but may relate to modulation in enzyme activity beyond mevalonate formation or to enzyme affinity. Obviously, further studies are needed to evaluate this concept.

There are a number of limitations in this study, including a small sample size and the open-label nature of the trial. Whether more subjects would have shown a difference is not known but is unlikely because the change in CoQ10 was small and the SD was not large. The open-label design of the trial appears not to be a factor because the effect of both simvastatin and atrovastatin on lipid levels were as expected and there were no subjective data evaluated in this study. However, the observed decrease in LDL by both drugs (>25%) is a good response to the doses used and may often be greater than what is seen at higher doses in many patients clinically. Furthermore, as observed in other studies, this decrease in LDL should have been sufficient to reduce CoQ10 concentrations as previously suggested.

The results of this study may have important clinical implications. In the recent light of renewed interest in natural or alternative medicine, administration of supplemental CoQl0 has drawn attention, especially in patients with cardiac disease.

Because CoQ10 is an antioxidant and is required for synthesis of ATP, decreased concentrations of CoQ10 may be of importance in patients with coronary artery disease and congestive heart failure. Therefore any therapy, such as HMG-CoA reductase inhibitors, that may further decrease CoQ10 especially in cardiac patients is of concern to health care practitioners. There has even been some suggestion that CoQl0 should be supplemented in patients receiving statin therapy. However, the data from our study suggest that this is not required because the synthesis of CoQ10 appears not to be affected by HMG-CoA reductase inhibitor therapy.

CONCLUSION

In conclusion, neither simvastatin nor atorvastatin decreased

CoQ10 concentrations despite significant decreases in TC and LDL levels in healthy subjects. They suggest that HMG-CoA reductase inhibitors do not decrease the synthesis of circulating CoQ10. This finding may have clinical implications in regard for the need to supplement CoQ10 in patients receiving HMG-CoA reductase inhibitor therapy.

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