Similar therapeutic serum levels attained with emulsified and oil-based preparations of coenzyme Q₁₀

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Studies of the therapeutic efficacy of coenzyme Q₁₀ (CoQ₁₀) have been confounded by the variable bioavailability of numerous CoQ₁₀ preparations. The aims of the present study were to determine the early serum levels attained by two different preparations of CoQ₁₀, a soybean oil-based preparation and a complex micelle emulsion and to assess whether these preparations of oral CoQ₁₀ influence plasma lipid profiles. Twelve healthy individuals received 300 mg CoQ₁₀ daily of either preparation for 7 days in a double-blind cross-over design with a 21-day washout period. Blood samples to determine serum levels of CoQ₁₀ and lipids were taken at baseline, after 24 h and 7 days. Both preparations induced significant increases in serum CoQ₁₀ levels at 24 h and 7 days. These were for soy oil: baseline 0.27 ± 0.03 mol/L, 24 h 0.50 ± 0.04 mol/L (180%) and 7 days 0.80 ± 0.05 mol/L (291%), mean ± SEM; for emulsion: baseline 0.29 ± 0.03 mol/L, 24 h 0.45 ± 0.03 mol/L (150%) and 7 days 0.79 ± 0.06 mol/L (270%). There were no significant differences between CoQ₁₀ levels for the two preparations at either time point. There was no change in any of the serum lipids following the 7 days treatment. We conclude that administration of either a soy oil suspension or a complex emulsion of CoQ₁₀ increases serum levels to the therapeutic range within 1 week.

Key words: Australia, coenzyme Q₁₀, double-blind crossover study, serum levels.

Introduction

Coenzyme Q₁₀ (CoQ₁₀), also known as ubiquinone, was discovered by Crane in 1957 and its structure described by Erickson et al. 1 year later. Although CoQ₁₀ has been used since the late 1960s as an anti-oxidant, it is only in the last two decades that it has been applied as a treatment for cardiac disorders, particularly congestive cardiac failure.

The highest concentrations of CoQ₁₀ are found in the most metabolically active organs, such as the heart, brain, kidney and liver. Within the cell, CoQ₁₀ is found in highest concentrations within the inner mitochondrial membrane, the area with the highest rate of free radical production. The content of CoQ₁₀ in tissues peaks in the early twenties and then gradually decreases with age. Coenzyme Q₁₀ has two key functions, first, as an integral component of the electron transfer chain that carries electrons from complex I and II to complex III to generate ATP and second, as a lipid-soluble anti-oxidant.

Many studies of the therapeutic efficacy of CoQ₁₀ have been confounded by the variable bioavailability of the various CoQ₁₀ preparations used. High serum levels early after administration are important in situations where there is limited time for CoQ₁₀ to be given, such as prior to cardiac surgery. In cardiac surgical patients CoQ₁₀ has been shown to have a beneficial effect when given for periods of 14 or 7 days preoperatively, but not when given for periods of 1 day or less. In the clinical setting where urgent cardiac surgery is mandated, logistic considerations frequently restrict the time available for CoQ₁₀ pretreatment. To improve the rate of absorption over that obtained from powder-based preparations new formulations have been produced including soy oil suspensions and more recently emulsified preparations. It has been reported that an emulsified CoQ₁₀ preparation can induce a rapid rise in serum levels. Therefore, as a prelude to a clinical trial in cardiac surgical patients, we compared the serum levels achieved by the emulsified preparation with those obtained with a soy oil preparation in healthy volunteers.

As CoQ₁₀ and cholesterol share a common synthetic pathway and because certain inhibitors of cholesterol synthesis (3-hydroxy-3-methylglutaryl 1 (HMG) CoA reductase inhibitors) are known to reduce serum CoQ₁₀ levels, we measured levels of plasma lipids before and after CoQ₁₀ administration to determine whether CoQ₁₀ therapy could influence cholesterol levels.

Methods

Study design

The study employed a double-blind cross-over design. The Alfred Hospital Human Ethics Review Committee approved the study protocol. Two different formulations of CoQ₁₀ were used, both containing 50 mg CoQ₁₀, packaged in soft gelatin capsules.
capsules. The first formulation contained CoQ10 dissolved in soybean oil (Blackmores, Sydney, Australia), and the second contained CoQ10 as a complex micelle in an emulsion encapsulated in a soft gelatin capsule (NDS, Sydney, Australia).

Twelve healthy, non-smoking volunteers were recruited from a local community of office workers and informed consent obtained. Exclusion criteria included current medication with either CoQ10 or other anti-oxidants. Each subject received a single morning dose of 300 mg daily of one preparation, with food, for a period of 7 days. A washout period of at least 3 weeks was allowed and the other preparation was given as before. The volunteers’ usual diet and exercise routines were maintained throughout the study period.

At the beginning of the trial, following an overnight fast baseline blood samples for levels of CoQ10 and cholesterol were taken. Dosing was then started and continued for a further 6 days. A second fasting blood sample was taken 24 h after the first dose. A final blood sample was taken 24 h after the final morning dose, again with overnight fasting. The researchers and subjects were blinded as to the identity of the preparations and the order in which they were taken. The subjects were questioned regarding side-effects of the medication.

Blood was stored in lithium-heparin tubes, which were then centrifuged for 20 min at 1000 g. The serum was separated and stored in Z serum clot activator tubes and kept at –80°C. Coenzyme Q10 was extracted from the serum using an alcohol/hexane technique and analysed using a high-performance liquid chromatographic method (HPLC), with CoQ6 as the internal standard (yeast-derived standard from Sigma-Aldrich, Castle Hill, NSW, Australia). The sample then underwent further centrifugation at 800 g, with reconstitution using ethanol and acetonitrile. Final levels were determined using 275 nm UV absorption spectrophotometry. Cholesterol, triglyceride and lipoprotein levels were determined in the baseline and final blood samples using standard colorimetric reflectance spectrophotometry.

**Statistical methods**

Data are presented as mean ± SEM. Comparisons between the two groups over time were made using repeated measures analysis of variance (ANOVA). For baseline values the Student’s t-test was used.

**Results**

Six females and six males aged 22–57 years (mean 32.9 ± 11.4) were enrolled. There was no significant difference in baseline serum CoQ10 levels between the two groups: soy oil, 0.27 ± 0.03 mol/L, and emulsion 0.29 ± 0.03 mol/L (P = 0.813). After 21 days washout between each period of dosing with either formulation there was no significant difference from baseline CoQ10 level (P = 0.291). Over the first 24 h both preparations produced similar significant increases in serum levels (P < 0.001): soy increased to 0.50 ± 0.04 mol/L (180% of baseline), and emulsion increased to 0.45 ± 0.03 mol/L (150% of baseline) (difference between the two preparations, P = 0.87). After 7 days both preparations produced similar (P = 0.67), threefold increases in serum levels: soy oil 0.80 ± 0.05 mol/L (291%) and emulsion 0.79 ± 0.06 mol/L (270%), both significantly above baseline levels (P < 0.001) (Fig. 1).

There was no significant sex difference in serum CoQ10 levels over the 7 days of dosing between the two preparations (P = 0.62). The 1-week levels were: for soy, males (0.75 ± 0.06 mol/L) and females (0.84 ± 0.10 mol/L) (P = 0.68); emulsion, males (0.90 ± 0.13 mol/L) and females (0.68 ± 0.06 mol/L) (P = 0.35).

Neither CoQ10 preparation induced any change in plasma total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) or HDL/LDL ratio (P = 0.33 or greater in all cases). (Fig. 2). No side-effects were reported by any of the participants during the study.

**Discussion**

The aim of the present study was to compare the serum levels attained by two preparations of CoQ10 in healthy individuals. We compared the serum CoQ10 levels attained early after administration of a soy oil-based preparation on a lipid emulsion of CoQ10. We found that both preparations produced 1.5- and threefold increases over baseline serum levels of CoQ10 after 24 h and 7 days therapy, respectively. Langsjoen has shown that clinical improvements in heart failure are attained when plasma CoQ10 levels are elevated to twice the normal baseline under conditions where metabolism and absorption of CoQ10 may be altered.15 Judy et al. demonstrated a relationship between changes in serum and tissue CoQ10 levels with benefits in myocardial protection in patients not in advanced heart failure.8 Therefore, we believe that for both preparations the serum levels attained over 7 days
All cases). Following 7 days of oral administration of 300 mg daily of either CoQ10 dissolved in soy or a CoQ10 emulsion (Figure 2), no significant differences were demonstrated in any case. (P = 0.33 or greater in all cases).

To assess the tissue levels in the heart attained by short-term CoQ10 therapy we recently gave CoQ10 to patients undergoing cardiac surgery and were able to obtain discarded atrial myocardial tissue at the time of surgery. We demonstrated that 7 days is an adequate dosing period with a soy oil-based CoQ10 preparation to double the levels of CoQ10 in both atrial myocardium and in isolated atrial mitochondria. Thus in high risk patients, such as the elderly or those with poor left ventricular function, who are undergoing cardiac surgery or other stressful cardiac interventions, any beneficial effects might be detectable after 7 days pretreatment with 300 mg CoQ10 per day in either emulsified or soy oil-based form.

The present study has several limitations. We used a short duration of therapy to correspond with current cardiac surgical practice where there is often limited time between scheduling for surgery and the operation, especially in cases of unstable angina. As we set out to explore early serum levels only three samples were taken, which precluded the calculation of full area under curve (AUC) for determination of bioavailability. Serum levels were likely to still be increasing at the end of this study.

There have been several trials investigating differences in bioavailability of various CoQ10 preparations. Wahlqvist et al. demonstrated the superiority of emulsified CoQ10 over powdered preparations. Weis et al. compared the bioavailability of four different preparations of CoQ10 and also demonstrated the superiority of the soy oil-based formulation over powder-filled capsules. A study by Chopra et al. suggested that a proprietary formulation of CoQ10 (Q-Gel; Tishcon, Westbury, NY, USA) had superior bioavailability after 21 days compared with CoQ10 powder and oil-based preparations.

Given the common synthetic pathway for coenzyme Q10 and cholesterol and the inhibitory effect on CoQ10 synthesis of the widely used cholesterol-lowering HMG CoA reductase inhibitors we were interested to determine if coenzyme Q10 might lower plasma cholesterol perhaps via a negative feedback effect. However, we found no effect of CoQ10 administration on LDL, HDL, triglycerides or total cholesterol. There is evidence of a beneficial effect of exogenous coenzyme Q10 on the resistance of lipoproteins to oxidation. However, we assessed only standard serum lipid profiles, and did not determine the ratio of oxidized to reduced cholesterol.

We conclude that both soy oil and emulsified CoQ10 preparations, after 7 days therapy, produce increases in serum CoQ10 levels that are similar and in the putative therapeutic range.

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References