Original Article

Similar therapeutic serum levels attained with emulsified and oil-based preparations of coenzyme Q_{10}

William Lyon BMBS, Olivier Van den Brink, Salvatore Pepe PhD, Michelle Wowk BSc, Silvana Marasco MBBS, FRACS and Franklin L Rosenfeldt MD, FRACS

Cardiac Surgical Research Unit, Alfred Hospital and Baker Medical Research Institute, Melbourne, Victoria, Australia

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 Q_{10}, double-blind crossover study, serum levels.

Introduction

Coenzyme Q_{10} (CoQ_{10}), also known as ubiquinone, was discovered by Crane in 1957[1] and its structure described by Erickson *et al*. 1 year later.[2] Although CoQ_{10} 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.[3,4]

The highest concentrations of CoQ_{10} are found in the most metabolically active organs, such as the heart, brain, kidney and liver.[5] Within the cell, CoQ_{10} is found in highest concentrations within the inner mitochondrial membrane, the area with the highest rate of free radical production.[6] The content of CoQ_{10} in tissues peaks in the early twenties and then gradually decreases with age.[7] Coenzyme Q_{10} 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.[6]

Many studies of the therapeutic efficacy of CoQ_{10} have been confounded by the variable bioavailability of the various CoQ_{10} preparations used. High serum levels early after administration are important in situations where there is limited time for CoQ_{10} to be given, such as prior to cardiac surgery. In cardiac surgical patients CoQ_{10} has been shown to have a beneficial effect when given for periods of 14[8] or 7 days preoperatively,[9] but not when given for periods of 1 day or less.[10] In the clinical setting where urgent cardiac surgery is mandated, logistic considerations frequently restrict the time available for CoQ_{10} pretreatment. To improve the rate of absorption over that obtained from powder-based preparations new formulations have been produced including soy oil suspensions[11] and more recently emulsified preparations.[12,13] It has been reported that an emulsified CoQ_{10} preparation can induce a rapid rise in serum levels.[12] 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 CoQ_{10} and cholesterol share a common synthetic pathway and because certain inhibitors of cholesterol synthesis (3-hydroxy-3-methylglutary 1 (HMG) CoA reductase inhibitors) are known to reduce serum CoQ_{10} levels,[14,15] we measured levels of plasma lipids before and after CoQ_{10} administration to determine whether CoQ_{10} 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 CoQ_{10} were used, both containing 50 mg CoQ_{10}, packaged in soft gelatin

Correspondence address: Associate Professor FL Rosenfeldt, Cardiac Surgical Research Unit, Department of Cardiothoracic Surgery, Alfred Hospital, Commercial Road, Prahran, Vic. 3181, Australia.
Tel: + 61 3 9276 3684; Fax: + 61 3 9276 2317
Email: F.Rosenfeldt@alfred.org.au
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capsules. The first formulation contained CoQ_{10} dissolved in soybean oil (Blackmores, Sydney, Australia), and the second contained CoQ_{10} 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 CoQ_{10} 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 CoQ_{10} 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 Q_{10} was extracted from the serum using an alcohol/hexane technique and analysed using a high-performance liquid chromatographic method (HPLC), with CoQ_6 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 CoQ_{10} 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 CoQ_{10} 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).

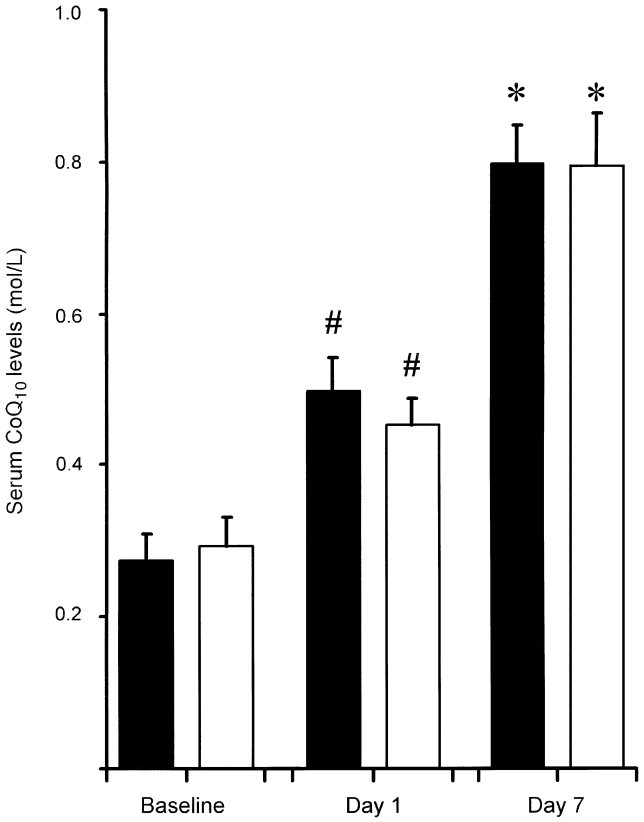

Figure 1. Mean serum coenzyme Q_{10} concentrations following oral administration of 300 mg daily of either CoQ_{10} dissolved in soy oil (Blackmores, Sydney, NSW, Australia), or emulsified (NDS Pty Ltd, Sydney, NSW, Australia) ($n = 12$ per treatment). #Difference in both groups between baseline and day 1; $P < 0.001$: *difference in both groups between baseline and day 7; $P < 0.001$ (mean ± SEM).

There was no significant sex difference in serum CoQ_{10} 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 CoQ_{10} 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 CoQ_{10} in healthy individuals. We compared the serum CoQ_{10} levels attained early after administration of a soy oil-based preparation on a lipid emulsion of CoQ_{10}. We found that both preparations produced 1.5- and threefold increases over baseline serum levels of CoQ_{10} after 24 h and 7 days therapy, respectively. Langsjoen has shown that clinical improvements in heart failure are attained when plasma CoQ_{10} levels are elevated to twice the normal baseline under conditions where metabolism and absorption of CoQ_{10} may be altered.[15] Judy *et al.* demonstrated a relationship between changes in serum and tissue CoQ_{10} 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

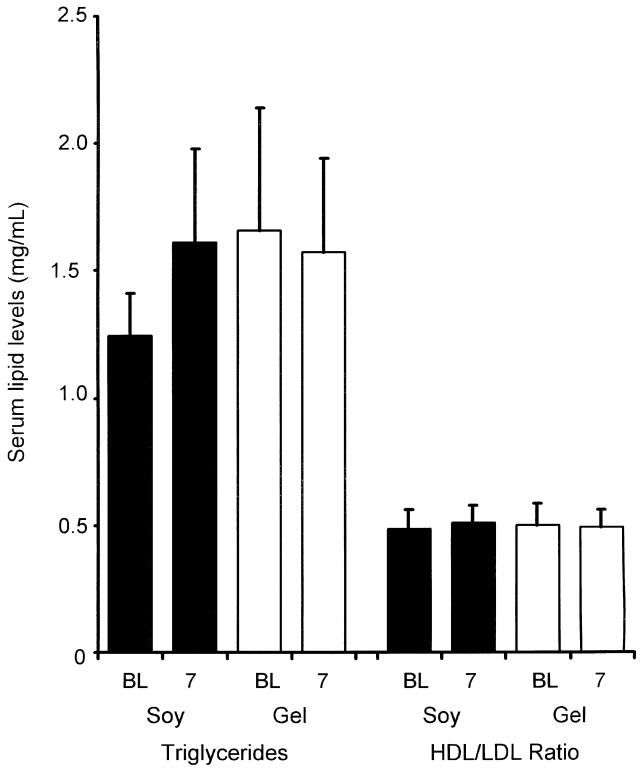

Figure 2. Plasma total cholesterol and high-density lipoprotein (HDL)/low-density lipoprotein (LDL) triglyceride ratio at baseline (BL) and following 7 days oral administration of 300 mg daily of either CoQ_{10} dissolved in soy or a CoQ_{10} emulsion (n = 12 per treatment). No significant differences were demonstrated in any case. (P = 0.33 or greater in all cases).

therapy in healthy individuals were in the therapeutic range as reported by Judy *et al*. and Langsjoen and Langsjoen.[8,15] Plasma CoQ_{10} levels had returned to baseline within 3 weeks of cessation of therapy with both preparations. We found that there was no effect of the sex of the subject on CoQ_{10} levels before or after therapy. Neither preparation caused any change in total serum cholesterol, HDL or LDL levels.

To assess the tissue levels in the heart attained by short-term CoQ_{10} therapy we recently gave CoQ_{10} 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 CoQ_{10} preparation to double the levels of CoQ_{10} in both atrial myocardium and in isolated atrial mitochondria.[16] 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 CoQ_{10} 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 CoQ_{10} preparations. Wahlqvist *et al.* demonstrated the superiority of emulsified CoQ_{10} over powdered preparations.[12] Weis *et al.* compared the bioavailability of four different preparations of CoQ_{10} and also demonstrated the superiority of the soy oil-based formulation over powder-filled capsules.[11] A study by Chopra *et al.* suggested that a proprietary formulation of CoQ_{10} (Q-Gel; Tishcon, Westbury, NY, USA) had superior bioavailability after 21 days compared with CoQ_{10} powder and oil-based preparations.[13]

Given the common synthetic pathway for coenzyme Q_{10} and cholesterol and the inhibitory effect on CoQ_{10} synthesis of the widely used cholesterol-lowering HMG CoA reductase inhibitors[17] we were interested to determine if coenzyme Q_{10} might lower plasma cholesterol perhaps via a negative feedback effect. However, we found no effect of CoQ_{10} administration on LDL, HDL, triglycerides or total cholesterol. There is evidence of a beneficial effect of exogenous coenzyme Q_{10} on the resistance of lipoproteins to oxidation.[18] 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 CoQ_{10} preparations, after 7 days therapy, produce increases in serum CoQ_{10} levels that are similar and in the putative therapeutic range.

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