



ELSEVIER

Nutrition Research 22 (2002) 919–929

**NUTRITION
RESEARCH**

www.elsevier.com/locate/nutres

Bioequivalence of coenzyme Q₁₀ from over-the-counter supplements

Michael V. Miles^{a,*}, Paul Horn^b, Lili Miles^c, Peter Tang^a, Paul Steele^c,
Ton DeGrauw^a

^a*Division of Child Neurology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, Ohio 45229-3039, USA*

^b*Department of Mathematical Sciences, University of Cincinnati College of Medicine, 231 Bethesda Avenue, Cincinnati, Ohio 45267-0559, USA*

^c*Department of Pathology and Laboratory Medicine, University of Cincinnati College of Medicine, 231 Bethesda Avenue, Cincinnati, Ohio 45267-0559, USA*

Received 30 November 2001; received in revised form 25 April 2002; accepted 27 April 2002

Abstract

The objective of this study was to compare the relative bioavailability of two new products with solubilized and non-solubilized over-the-counter (OTC) coenzyme Q₁₀ products. Nine healthy adults were given single 180 mg doses of each coenzyme Q₁₀ formulation at two week intervals. A commercially-marketed, non-solubilized Q₁₀ powder formulation (product D) was only minimally absorbed, and was excluded from the analysis of data. ANOVA comparison of maximum plasma concentrations (C_{\max}), time of maximum concentrations (t_{\max}), areas under the concentration-time curves from times zero to 144 hours post dose (AUC_{0-144h}), and areas under the concentration-time curves from times zero to infinity ($AUC_{0-\infty}$) were not significantly different ($P > 0.05$) between test products A (LiQ-10TM) and B (Q-NolTM) and the reference product C (UbiQGel[®]). The upper limits of the 90% confidence intervals of the log-transformed ratios (A:C and B:C) of C_{\max} , AUC_{0-144h} , and $AUC_{0-\infty}$ were >1.25 for both test products, but significant ($P < 0.05$) only for the B:C AUC_{0-144h} . The results of this study indicate that LiQ-10TM has increased bioequivalence compared to the reference product, but did not reach statistical significance. Q-NolTM has increased bioavailability compared to the reference product ($P < 0.05$). © 2002 Elsevier Science Inc. All rights reserved.

Keywords: Coenzyme Q₁₀; Ubiquinone; Ubiquinol; Ubidecarenone; Bioequivalence; Bioavailability

* Corresponding author. Tel.: +1-513-636-7871; fax: +1-513-636-3980.

E-mail address: m.miles@chmcc.org (M.V. Miles).

1. Introduction

Coenzyme Q₁₀ (ubiquinone or ubidecarenone) is an endogenous enzyme cofactor that is produced in all living cells in humans. Coenzyme Q₁₀ functions to promote the proton/electron translocation in mitochondria and lysosomes [1,2], protects mitochondria from free radical damage [3,4], may play a role in the permeability transition of the inner mitochondrial membrane [5], and is thought to be capable of preventing programmed cell death or apoptosis [6]. Recently interest in coenzyme Q₁₀ has increased because of evidence that it may function together with α -tocopherol in protecting the function of biological membranes [7], recycling α -tocopherol by sparing or regeneration [8], preventing the prooxidant effects of α -tocopherol [9], and providing lipoprotein with increased resistance to oxidation [9,10].

Coenzyme Q₁₀, which is marketed in the USA as an over-the-counter (OTC) dietary supplement, is a useful therapeutic agent for certain conditions associated with increased oxidative stress. In a recent review, Mongthuong and colleagues concluded that coenzyme Q₁₀ may be recommended as adjuvant therapy for chronic heart failure [11]. Preliminary studies suggest benefits from coenzyme Q₁₀ supplementation following cardiac surgery [12,13], in patients with chronic renal failure [14], and in patients with mitochondrial cytopathies [15–17]. A large, multicenter, randomized placebo-controlled trial recently reported benefits from coenzyme Q₁₀ supplementation in patients with Huntington's disease [18].

The absolute bioavailability of coenzyme Q₁₀ is unknown. Coenzyme Q₁₀ is strongly lipophilic, practically insoluble in aqueous solution, and has poor bioavailability in humans. The importance of product formulation was recognized early in the development of coenzyme Q₁₀ preparations [19]. Studies which attempted to improve coenzyme Q₁₀ bioavailability with emulsifying agents and oil-based vehicles had limited success improving bioavailability [20–21]. A fully-solubilized coenzyme Q₁₀ formulation was compared with two other preparations, and found to provide a 2.5 to three-fold increase in bioavailability [22]. The fully-solubilized product in that study was selected as the reference product for the current study (product C), because it appears to have the highest bioavailability of currently marketed Q₁₀ OTC products.

The purpose of this study was to compare the relative bioavailability (or bioequivalence) of four coenzyme Q₁₀ formulations. Specifically, the relative bioequivalence of two newly developed formulations, i.e. a liquid containing solubilized coenzyme Q₁₀ (product A or LiQ-10TM) and a soft capsule containing ubiquinol (the reduced form of coenzyme Q₁₀) (product B or Q-No1TM), are compared with two marketed OTC products, i.e. one containing fully-solubilized coenzyme Q₁₀ (product C or UbiQGel[®]) in the oxidized form (ubiquinone) and the other a commercial hard capsule product (product D) containing non-solubilized Q₁₀ powder. The secondary aim of this study was to compare subject tolerance of these coenzyme Q₁₀ products.

2. Materials and methods

2.1. Subjects

This study was approved by the Institutional Review Board of the Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA. Written informed consent was obtained

from all subjects. Thirteen healthy adult volunteers were enrolled into this study. The results of routine laboratory tests, including complete blood count, chemistry profile, lipid profile, and urinalysis, were within the normal ranges. Volunteers had no histories of diseases which might affect coenzyme Q₁₀ absorption. No subjects were taking supplements of coenzyme Q₁₀ for at least four weeks prior to the study, or other vitamin supplements for at least two weeks prior to the study. None had taken an investigational drug for at least one month before this study.

2.2. Study design

The first phase of this study was a run-in period in which a 180 mg dose of product D, a commercial product containing non-solubilized coenzyme Q₁₀ powder in a hard capsule (30 mg/capsule), was administered to each subject. A previous study reported that granular, non-solubilized coenzyme Q₁₀ was minimally absorbed in adults following a single dose [21]. Product D was tested to rule out the possibility of aberrant coenzyme Q₁₀ absorption by any subject, and to confirm the poor absorption characteristics of non-solubilized coenzyme Q₁₀ in a crystalline or powder formulation.

Two weeks following the run-in phase a single dose, randomized, crossover study of three products was conducted at the Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA. Test product A, LiQ-10™ (10 mg ubiquinone per mL; Control #0061–0070, Tishcon Corp., Westbury, NY, USA), is a liquid syrup formulation which contains solubilized coenzyme Q₁₀ in the oxidized form. Test product B, Q-Nol™ (30 mg per capsule; Control #0041-E-0070, Tishcon Corp., Westbury, NY, USA) is a soft gel capsule formulation containing coenzyme Q₁₀ in the reduced form (ubiquinol). Test product C (the control formulation), UbiQGel® (30 mg ubiquinone/capsule; Control #0651–0800, Tishcon Corp., Westbury, NY, USA), is a marketed soft gel capsule containing solubilized coenzyme Q₁₀ in the oxidized form. Single 180 mg doses of each formulation were administered in random sequence separated by a two week washout interval. Randomization was determined using a random numbers generator.

Before each study phase all subjects fasted for at least ten hours prior to the coenzyme Q₁₀ dose, and continued to fast for the first four hours following each dose. Doses were administered with 240 mL of water at approximately 8:00 AM immediately following collection of a baseline blood sample. Lipid profiles were also tested before each dose to insure the fasting state of each volunteer. Following each coenzyme Q₁₀ dose ten blood samples were collected during the subsequent 144 hours (2.0, 4.0, 6.0, 8.0, 10, 12, 24, 48, 96, and 144 hours post dose).

During the first 12 hours of each study phase the subjects remained in the medical center. Two cafeteria-style meals were provided at approximately 12:30 PM and 6:00 PM. Subjects were permitted to leave the medical center after the first 12 hours following each dose, but were required to return at the scheduled times for additional blood sample collection. The remaining blood samples (from 24 hours through 144 hours) were collected between 7:30 AM and 9:00 AM after overnight fasting.

2.3. Sample collection and processing

Blood specimens were collected from the antecubital vein into glass vacuum tubes containing sodium heparin. Blood was immediately refrigerated, then tubes were centrifuged within one hour of collection at 2,000 g for ten minutes at +5° C. Plasma was immediately transferred to a pre-labeled, two mL screw-capped polypropylene tubes, then stored at –80° C until analysis.

2.4. Coenzyme Q₁₀ analysis

Plasma samples were analyzed for total plasma coenzyme Q₁₀ concentrations in the Clinical Neuropharmacology Laboratory of the Cincinnati Children's Hospital Medical Center using a previously validated high performance liquid chromatography (HPLC) procedure with electrochemical detection [23]. In brief this new method measures oxidized, reduced, and total coenzyme Q₁₀ concentrations in plasma over an analytical range from 0.01 to 4.0 mg/L. The intra-assay and inter-assay CVs were 1.2–4.9% across this concentration range. This optimized method provides reliable determination of coenzyme Q₁₀ in plasma.

All other tests (chemistry profiles, complete blood counts, lipid profiles, and urinalysis) were provided by the Clinical Laboratory Service of the Cincinnati Children's Hospital Medical Center.

2.5. Pharmacokinetics analysis

The pharmacokinetics of each coenzyme Q₁₀ product was determined by the noncompartmental method. Following each dose the increase in plasma concentration above the predose endogenous coenzyme Q₁₀ concentration was used to calculate pharmacokinetic parameters. Maximum plasma coenzyme Q₁₀ concentration (C_{\max}), time of maximum concentration (t_{\max}), and area-under-the-concentration curve (AUC_{0-144h} and $AUC_{0-\infty}$) were determined using WinNonlin™ software (version 1.5, Pharsight Corp., Mountain View, CA, USA).

2.6. Statistical analysis

All of the response variables were transformed to the (natural) logarithmic scale. Two-way mixed model Analyses of Variance were conducted on each of the response variables C_{\max} , AUC_{0-144h} , $AUC_{0-\infty}$, and the concentrations at the each of the eleven time points (baseline and ten post treatment). The two factors were product (fixed effect) and subject (random effect). The period and sequence factors were ignored for this part of the analysis.

A mixed model procedure (SAS® PROC MIXED, SAS Institute Inc., Cary, NC, USA) was used for assessing bioequivalence in this crossover design study [24]. This procedure provides for the direct calculation of the Schuirmann 90% confidence intervals [24]. Bioequivalence was established if the 90% confidence interval of this difference, back-transformed using exponentiation, was contained in the interval (0.8, 1.25).

2.7. Safety assessments

Following each coenzyme Q₁₀ dose subjects were required to record whether or not they had experienced any untoward effects. A standard form was completed and signed by each subject to document whether or not ill effects were noted.

3. Results

3.1. Subject demographics and discontinuations

Nine subjects (eight M/one F), ranging in age from 23 to 56 y (median 36 y) and weighing 55 kg to 103 kg (median 87 kg), completed all four phases of the study. The weight-adjusted median dose of coenzyme Q₁₀ administered was 2.1 mg/kg (range 1.8 to 3.3 mg/kg).

Thirteen subjects were enrolled into this study. Three subjects failed to complete the study for personal reasons unrelated to the study products. A fourth individual was considered to be noncompliant with the study protocol because of intermittently high triacylglycerol (> 400 mg/dL) and total cholesterol (> 250 mg/dL) concentrations. Data from these four subjects were excluded from the analysis. All other chemistry, blood, and lipid profile results were within the normal range for healthy adults.

3.2. Bioequivalence comparisons

Comparison of predose coenzyme Q₁₀ concentrations during each study phase indicated that plasma concentrations had returned to baseline (endogenous) concentrations, and there was no indication of carryover effect from the previous dose (Fig. 1). The absorption curve following administration of the non-solubilized powder formulation (product D) confirmed that all subjects had minimal absorption of coenzyme Q₁₀ (Fig. 2). Five of nine subjects had a maximum coenzyme Q₁₀ concentration (C_{\max}) \leq 0.1 $\mu\text{g/mL}$ above baseline (predose) concentration. Only one individual had a C_{\max} > 0.2 $\mu\text{g/mL}$ above the baseline concentration, i.e. 0.23 $\mu\text{g/mL}$, following the dose of non-solubilized coenzyme Q₁₀. These data, which confirmed previous findings [21], were excluded from the final bioequivalence analysis.

Significantly increased coenzyme Q₁₀ concentrations (greater than the reference product C) occurred for product B at $C_{2\text{h}}$ (0.158 $\mu\text{g/mL}$, $P = .018$), $C_{8\text{h}}$ (0.163 $\mu\text{g/mL}$, $P = .047$), $C_{10\text{h}}$ (0.133 $\mu\text{g/mL}$, $P = .023$), $C_{12\text{h}}$ (0.144 $\mu\text{g/mL}$, $P = .026$) (Fig. 2). Coenzyme Q₁₀ concentrations following the dose of product A were significantly increased at $C_{10\text{h}}$ (0.157 $\mu\text{g/mL}$, $P = .009$) and $C_{12\text{h}}$ (0.140 $\mu\text{g/mL}$, $P = .029$) (Fig. 2). It should be noted, however, that if the nominal level of .05 is adjusted for the 30 paired comparisons, using a Bonferroni correction, then none of the above differences is significant at an experiment-wise error rate equal to .05.

The t_{\max} values for products A, B, and C were very consistent. All subjects, except two for product A, one for product B, and one for product C, had t_{\max} occur six hours after each coenzyme Q₁₀ dose (Table 1). The mean C_{\max} of product A is similar to product C, but

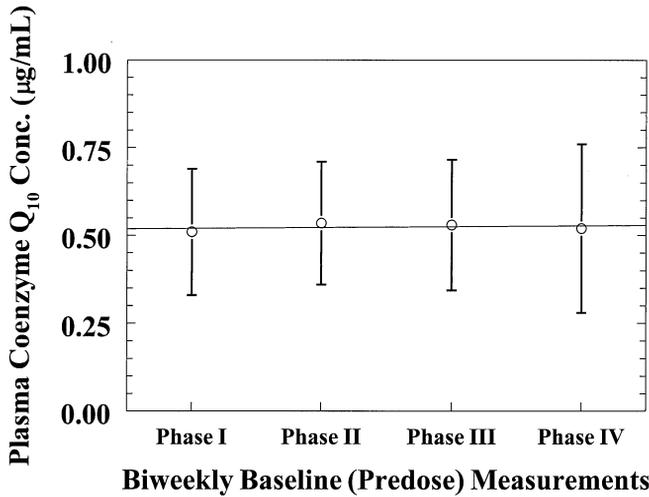


Fig. 1. Comparison of mean (SD) coenzyme Q₁₀ plasma concentrations prior to the administration of coenzyme Q₁₀ test doses during the run-in period (phase I) and each study phase (phases II-IV). No significant difference exists between these concentrations. The regression line is provided to show the constancy of baseline (endogenous) coenzyme Q₁₀ plasma concentrations throughout the study.

product B is approximately 25% higher than product C (Tables 1 and 2). This difference did not reach statistical significance, however, probably due to the limited number of subjects. The upper limits of the 90% confidence intervals of the log-transformed ratios of C_{max}, AUC_{0–144h}, and AUC_{0–∞} for products A and B were >1.25, although statistical significance is reached only for AUC_{0–144h} of product B (*P* < 0.05) (Table 2). The 90% confidence interval of C_{12h} is also significantly increased for product B (*P* < 0.05) (Table 2).

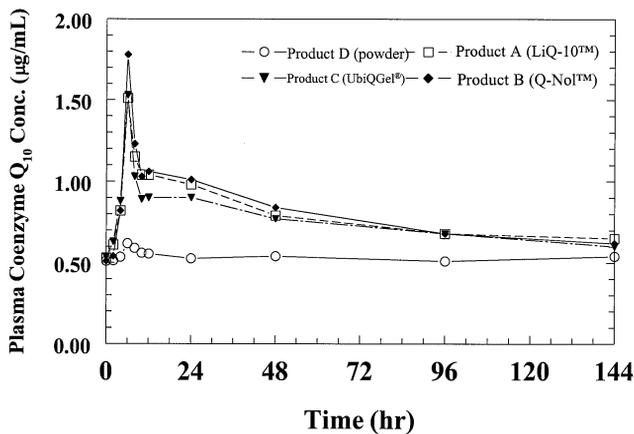


Fig. 2. Comparison of mean (SD) coenzyme Q₁₀ plasma concentrations just prior to and following each coenzyme Q₁₀ study dose. Coenzyme Q₁₀ concentrations following administration of the non-solubilized powder formulation (product D) were not included in the statistical analysis to the other products, because of the minimal change from baseline which occurred following administration.

Table 1

Changes in pharmacokinetic parameters (mean \pm SD) of coenzyme Q₁₀ measured above baseline concentrations following administration of single 180 mg doses of four coenzyme Q₁₀ products to nine healthy adults

Product	C _{max} (mg L ⁻¹)	t _{max} (h)	C _{12h} (mg L ⁻¹)	AUC _{0–144h} (mg · h L ⁻¹)	AUC _{0–∞} (mg · h L ⁻¹)
A (LiQ-10™)	1.03 \pm 0.37	6.2 \pm 1.6	0.51 \pm 0.13 ^a	35.82 \pm 14.15	51.67 \pm 38.01
B (Q-NoI™)	1.27 \pm 0.66	8.1 \pm 6.3	0.55 \pm 0.19 ^a	41.09 \pm 21.82	55.26 \pm 34.53
C (UbiQGel®)	1.03 \pm 0.50	5.8 \pm 0.7	0.37 \pm 0.06	30.0 \pm 9.33	38.80 \pm 17.33
D (Q ₁₀ powder)	0.12 \pm (0.05)	6.7 \pm 1.0	0.05 \pm 0.06	2.81 \pm 3.46	—

^a C_{12h} for product A and product B compared with C_{12h} for reference product C ($P < 0.05$).

3.3. Safety

No significant adverse effects were reported during this study. Two subjects reported mild stomach discomfort approximately 30 minutes after the coenzyme Q₁₀ dose, each of which lasted less than 1 hour. One of these two subjects experienced mild gastric discomfort on two separate occasions, once following the liquid formulation (product A) and again following the reduced coenzyme Q₁₀ formulation (product B). The other individual experienced gastric discomfort only after taking the liquid formulation (product A). No additional treatment was required for either of these subjects, and both individuals completed all four phases of the study.

4. Discussion

The safety profile of coenzyme Q₁₀ appears to be quite good. Mild gastrointestinal disturbances have been reported by other studies, but rarely required discontinuation of coenzyme Q₁₀ supplementation. All subjects who participated in this study tolerated 180 mg

Table 2

Statistical analysis of bioequivalence of log-transformed C_{max}, C_{12h}, AUC_{0–144h}, and AUC_{0–∞h} of two coenzyme Q₁₀ products (A or LiQ-10™, B or Q-NoI™) vs. control (reference) product C (UbiQGel®) after administration of 180 mg as single doses to nine healthy adults

Test vs. control	C _{max}		C _{12h}		AUC _{0–144h}		AUC _{0–∞}	
	A vs. C	B vs. C	A vs. C	B vs. C	A vs. C	B vs. C	A vs. C	B vs. C
Geometric mean ratio (test/control)	1.06	1.24	1.15	1.16	1.14	1.27	1.18	1.32
Range (arithmetic ratios)	0.42–2.38	0.77–2.36	1.94–3.13	2.56–5.64	0.88–2.07	0.89–1.28	0.91–1.32	0.77–1.41
90% Confidence Interval	0.82–1.36	0.96–1.61	1.02–1.27	1.03–1.29*	0.89–1.34	1.05–1.59*	0.81–1.59	0.99–1.95

* $P < 0.05$

doses of coenzyme Q₁₀ very well, even though all doses were taken after an overnight fast with 240 mL of water.

Although the safety profile of coenzyme Q₁₀ appears to be good at lower doses (<100 mg/day), adverse effects have been associated with higher doses. One report suggested that treatment with coenzyme Q₁₀ prior to intense exercise caused increased plasma creatine kinase and cellular damage [25]. However, other reports involving coenzyme Q₁₀ supplementation in endurance trained athletes and untrained men do not support these findings [26–28]. One placebo-controlled, double blinded trial evaluated the effects of coenzyme Q₁₀ and α -tocopherol supplementation before and after running a marathon [29]. The increase in baseline creatine kinase was somewhat less in the coenzyme Q₁₀ supplemented group than in the placebo group [29].

Larger doses of coenzyme Q₁₀, from 200 mg/day to 1,200 mg/day, have been administered chronically to patients without significant adverse events [18,30–32]. Langsjoen and colleagues reported that coenzyme Q₁₀ dosing (mean 242 mg/day, range 75 mg/day to 600 mg/day) by 424 cardiovascular disease patients caused no apparent side effects, except for one individual who experienced nausea [30]. Feigin and colleagues studied the effects of high dose (600 mg/day to 1,200 mg/day) coenzyme Q₁₀ in 10 patients with Huntington's Disease [31]. Two individuals experienced heartburn and headache, which were graded as mild to moderate severity [31]. None of the adverse events required reduction or discontinuation of coenzyme Q₁₀ [31]. Shults and colleagues studied the tolerability of coenzyme Q₁₀ in 15 patients with Parkinson's Disease [32]. Dosages of coenzyme Q₁₀ ranged from 400 mg/day to 800 mg/day [32]. None of the patients reported adverse effects [32]. Two patients, taking 800 mg/day, were observed to have three to five hyaline casts per low power field and trace protein on repeat urinalysis [32]. No abnormalities were noted on follow-up after discontinuation of coenzyme Q₁₀ [32]. These authors recommend prudent monitoring of renal function with coenzyme Q₁₀ dosing greater than 600 mg/day [32]. In addition, taking coenzyme Q₁₀ with food seems to be advisable for individuals who are sensitive to the gastrointestinal effects, although it should be noted that the effect of food on coenzyme Q₁₀ absorption has not been clearly delineated.

Assessment of coenzyme Q₁₀ bioequivalence must take into account endogenous concentrations of this substance. Endogenous concentrations of coenzyme Q₁₀ in plasma are relatively stable over time. In the current study predose coenzyme Q₁₀ concentrations were unchanged during the study (Fig. 1). In addition the stability of endogenous coenzyme Q₁₀ concentrations can be observed between 24 hours and 144 hours following administration of product D, which was minimally absorbed (Fig. 2).

It has been reported that the average dietary intake of coenzyme Q₁₀ in Denmark is only three to five mg per day [33]. A variety of food items were tested for coenzyme Q₁₀ content, and it was found that certain meats, i.e. pork, poultry, and beef, had somewhat higher amounts of coenzyme Q₁₀ than fruit and vegetables [33]. However, normal dietary intake had little effect on coenzyme Q₁₀ concentrations, and would be unlikely to affect bioequivalence estimates of the current study.

The importance of product formulation on coenzyme Q₁₀ bioavailability has been suggested in earlier studies. In the present study product D, a marketed product containing non-solubilized coenzyme Q₁₀ powder, was observed to be only minimally absorbed fol-

lowing a 180 mg dose (Fig. 2). Based upon these results it can be predicted that only slight increases in coenzyme Q₁₀ plasma concentration will occur with chronic supplementation of a product containing this non-solubilized powder form of Q₁₀. All clinicians need to be aware of this bioavailability problem, because many of the OTC products marketed in the USA and other countries contain this non-solubilized Q₁₀ powder. Dietitians and nutritionists should educate health care providers and the general public about these product differences.

Because of the insolubility of coenzyme Q₁₀ in water, a variety of formulations have been developed to solubilize the agent and promote absorption. An earlier study tested the bioequivalence of four oral coenzyme Q₁₀ formulations in ten healthy volunteers, and reported a 35% increase in area under the concentration-time curve (AUC) following administration of coenzyme Q₁₀ in soy bean oil vs. various emulsifying agents [20]. In another report following 4 weeks of continuous coenzyme Q₁₀ dosing (120 mg/day), Chopra et al found a 2.5- to three-fold increase in bioavailability for a formulation containing fully-solubilized coenzyme Q₁₀ (Q-Gel™) compared to other commercial products [22]. The Q-Gel™ formulation used in their study is identical to product C (UbiQGel®) selected as the reference product for the current study.

The current study shows that the new formulation (product B or Q-NoI™) of coenzyme Q₁₀, which contains the reduced form (ubiquinol), has increased bioavailability compared to the fully-solubilized reference formulation. The liquid preparation (product A or LiQ-10™), has increased bioequivalence compared to the reference product C, but did not reach a statistically significant difference. The liquid formulation may be useful for individuals who have difficulty or are unable to swallow solid formulations. Further studies are needed to determine whether these new products will provide significantly higher coenzyme Q₁₀ concentrations with chronic dosing. All four products tested were well tolerated in fasting adults. Because of inter-individual and inter-product variability in coenzyme Q₁₀ absorption, it is advisable that coenzyme Q₁₀ plasma concentrations be monitored in patients receiving supplementation to assure dosing adequacy and document compliance.

Acknowledgments

Dr. M. Miles was the principal investigator of this study, recruiting subjects, and pharmacokinetic data analysis. Dr. P. Horn analyzed data. Dr. L. Miles processed samples and helped write the final manuscript. Dr. P. Tang performed the plasma coenzyme Q₁₀ analysis. Dr. P. Steele provided laboratory screening and lipid profile testing. Dr. T. DeGrauw provided medical screening and supervision. The products tested in this study were provided by the Tishcon Corporation, Westbury, NY, USA. This study supported in part by a grant from the Tishcon Corporation, Westbury, NY, USA. Dr. M. Miles has served as a consultant for the Tishcon Corporation in the past. None of the authors has any financial or employment relationship with the Tishcon Corporation.

References

- [1] Crane FL, Navas P. The diversity of coenzyme Q function. *Molec Aspects Med* 1997;18(Suppl.):s1–6.

- [2] Gille L, Nohl H. The existence of a lysosomal redox chain and the role of ubiquinone. *Arch Biochem Biophys* 2000;375:347–54.
- [3] Lass A, Sohal RS. Effect of coenzyme Q₁₀ and α -tocopherol content of mitochondria on the production of superoxide anion radicals. *FASEB J* 2000;14:87–94.
- [4] Schöpfer F, Riobó N, Carreras MC, Alvarez B, Radi B, Cadena E, et al. Oxidation of ubiquinol by peroxynitrite: implications for protection of mitochondria against nitrosative damage. *Biochem J* 2000;349:35–42.
- [5] Fontaine E, Ichas F, Bernardi P. A ubiquinone-binding site regulates the mitochondrial permeability transition pore. *J Biol Chem* 1998;273:25734–40.
- [6] Kagen T, Davis C, Lin L, Zakeri Z. Coenzyme Q₁₀ can in some circumstances block apoptosis, and this effect is mediated through mitochondria. *Ann N Y Acad Sci* 1999;887:31–47.
- [7] Kagan VE, Fabisiak JP, Quinn PJ. Coenzyme Q, and vitamin E need each other as antioxidants. *Protoplasma* 2000;214:11–8.
- [8] Lass A, Forster MJ, Sohal RS. Effects of coenzyme Q₁₀ and α -tocopherol administration on their tissue concentrations in the mouse: elevation of mitochondrial α -tocopherol by coenzyme Q₁₀. *Free Rad Biol Med* 1999;26:1375–82.
- [9] Thomas SR, Neuzil J, Stocker R. Cosupplementation with coenzyme Q prevents the prooxidant effect of α -tocopherol and increases the resistance of LDL to transition metal-dependent oxidation initiation. *Arterioscler Thromb Vasc Biol* 1996;16:687–96.
- [10] Shi H, Noguchi N, Niki E. Comparative study on dynamics of antioxidative action of α -tocopherol hydroquinone, ubiquinol, and α -tocopherol against lipid peroxidation. *Free Rad Biol Med* 1999;26:1375–82.
- [11] Mongthuong TT, Mitchell TM, Kennedy DT, Giles GT. Role of coenzyme Q₁₀ in chronic heart failure, angina, and hypertension. *Pharmacotherapy* 2001;21:797–806.
- [12] Maulik N, Yoshida T, Engelman RM, Bagchi D, Otani H, Das DK. Dietary coenzyme Q₁₀ supplement renders swine hearts resistant to ischemia-reperfusion injury. *Am J Physiol Heart Circ Physiol* 2000;278:H1084–90.
- [13] Zhou M, Zhi Q, Tang Y, Yu D, Han J. Effects of coenzyme Q₁₀ on myocardial protection during cardiac valve replacement and scavenging free radical activity in vitro. *J Cardiovasc Surg* 1999;40:355–61.
- [14] Singh RB, Khanna HK, Niaz MA. Randomized, double-blind placebo-controlled trial of coenzyme Q₁₀ in chronic renal failure: discovery of a new role. *J Nutri Envir Med* 2000;10:281–8.
- [15] Chan A, Reichmann H, Kögel A, Beck A, Gold R. Metabolic changes in patients with mitochondrial myopathies and effects of coenzyme Q₁₀ therapy. *J Neurol* 1998;245:681–5.
- [16] Chen R, Huang C, Chu N. Coenzyme Q₁₀ treatment in mitochondrial encephalomyopathies. *Eur Neurol* 1997;37:212–8.
- [17] Barbiroli B, Frassinetti C, Marinelli P, Iotti S, Lodi R, Cortelli P, Montagna P. Coenzyme Q₁₀ improves mitochondrial respiration in patients with mitochondrial cytopathies. An *in vivo* study on brain, and skeletal muscle by phosphorus magnetic resonance spectroscopy. *Cell Molec Biol* 1997;43:741–9.
- [18] The Huntington Study Group. A randomized, placebo-controlled trial of coenzyme Q₁₀, and remacemide in Huntington's disease. *Neurology* 2001;57:397–404.
- [19] Kishi H, Kanamori N, Nishii S, Hiraoka E, Okamoto T, Kishi T. Metabolism of exogenous coenzyme Q₁₀ in vivo and the bioavailability of coenzyme Q₁₀ preparations in Japan. In: *Biomedical and clinical aspects of coenzyme Q₁₀*. New York: Elsevier Science Publishers, 1983. p. 131–42.
- [20] Weis M, Mortensen SA, Rassing MR, Moller-Sønnergaard J, Poulsen G, Rasmussen SN. Bioavailability of four oral coenzyme Q₁₀ formulations in healthy volunteers. *Molec Aspects Med* 1994;15(Suppl.):s273–80.
- [21] Kaikkonen J, Nyssönen K, Porkkala-Sarataho E, et al. Effect of oral coenzyme Q₁₀ supplementation on the oxidation resistance of human VLDL+LDL fractions: absorption and antioxidative properties of oil and granule-based preparations. *Free Rad Biol Med* 1997;22:1195–202.
- [22] Chopra R, Goldman R, Sinatra ST, Bhagavan N. Relative bioavailability of coenzyme Q₁₀ formulations in human subjects. *Internat J Vit Nutr Res* 1997;68:109–13.

- [23] Tang PH, Miles MV, DeGrauw A, Bean J, Pesce A. HPLC analysis of reduced, and oxidized coenzyme Q₁₀ in human plasma. *Clin Chem* 2001;47:256–65.
- [24] Le Roux Y, Guimart C, Tenenhaus M. Use of the repeated cross-over design in assessing bioequivalence: (within and between subjects variability—Schuirmann Confidence Intervals estimation). *Eur J Drug Metab Pharmacol* 1998;23:339–45.
- [25] Malm C, Svensson M, Sjöberg B, Ekblom B, Sjödin B. Supplementation with ubiquinone-10 causes cellular damage during intense exercise. *Acta Physiol Scand* 1996;157:511–2.
- [26] Laaksonen R, Fogelholm M, Himberg JJ, Laakso J, Salorinne Y. Ubiquinone supplementation and exercise capacity in trained young and older men. *Eur J Appl Physiol* 1995;72:95–100.
- [27] Weston SB, Zhou S, Weatherby RP, Robson SJ. Does exogenous coenzyme Q₁₀ affect aerobic capacity in endurance athletes? *Int J Sport Nutr* 1997;7:197–206.
- [28] Ylikoski T, Piirainen J, Hanninen O, Penttinen J. The effect of coenzyme Q₁₀ on the exercise performance of cross-country skiers. *Mol Aspects Med* 1997;18(Suppl.):S283–90.
- [29] Kaikkonen J, Kosonen L, Nyysönen K, Porkkala-Sarataho E, Poulsen HE, Salonen R, et al. Effect of combined coenzyme Q₁₀ and d- α -tocopheryl acetate supplementation on exercise-induced lipid peroxidation and muscular damage: a placebo-controlled double-blind study in marathon runners. *Free Rad Res* 1998;29:85–92.
- [30] Langsjoen H, Langsjoen P, Willis R, Folkers K. Usefulness of coenzyme Q₁₀ in clinical cardiology: a long term-study. *Molec Aspects Med* 1994;15(Suppl.):s165–75.
- [31] Feigin A, Kiebertz K, Como P, Hickey C, Claude K, Abwender D, et al. Assessment of coenzyme Q₁₀ tolerability in Huntington's Disease. *Movement Disorders* 1996;11:321–3.
- [32] Shults CW, Beal MF, Fontaine D, Nakano K, Haas RH. Absorption, tolerability, and effects on mitochondrial activity of oral coenzyme Q₁₀ in parkinsonian patients. *Neurology* 1998;50:793–5.
- [33] Weber C, Bysted A, Hølmer G. Coenzyme Q₁₀ in the diet-daily intake, and relative bioavailability. *Molec Aspects Med* 1997;18(Suppl.):s251–4.