COENZYME Q-10 AND CARDIOVASCULAR HEALTH

Kenneth Jones, Kerry Hughes, BSc, Laurie Mischley, ND, and Dennis J. McKenna, PhD

Kenneth Jones is president of Armana Research in Gibsons, British Columbia, Canada. Kerry Hughes is president of Ethnopharm Consulting in San Rafael, Calif. Laurie Mischley is completing her residency in naturopathic medicine at University Health Clinic in Seattle, Wash. Dennis J. McKenna is executive director of the Institute for Natural Products Research in Marine on St. Croix, Minn, and a senior lecturer at the Center for Spirituality and Healing at the University of Minnesota, Minneapolis.

InnoVision Communications is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The learner should study the article and its figures or tables, if any, then complete the self-evaluation at the end of the activity. The activity and self-evaluation are expected to take a maximum of 1 hour.

OBJECTIVES
Upon completion of this article, participants should be able to do the following:

1. Comprehend the functions of CoQ-10 in mammalian metabolism.
2. Evaluate the preclinical and clinical literature on CoQ-10 supplementation that supports (or in some cases does not support) its therapeutic uses.
3. Apply this knowledge of potential therapeutic applications and health benefits of CoQ-10 supplementation to clinical practice.
4. Understand the dosage, formulation and safety issues related to the use of CoQ10 as a supplement.

To date, the main application of CoQ-10 has been the treatment of cardiological disease, including congestive heart failure, hypertension, angina pectoris, and arrhythmias.1-3 Doses were usually 100 mg/d,3 and in some trials up to 240 mg/d.1 Male patients with effort angina and ischemic heart disease have shown normal levels of CoQ-10 in muscles of the diaphragm, gastrocnemius, and vastus lateralis, but levels in intercostal muscles were lower compared to those of healthy individuals. Levels of endogenous CoQ-10 and succinate-CoQ-10 oxireductase, key components of complex II of the mitochondrial respiratory chain, are reported to be depressed in myocardial tissue and blood samples of patients with cardiomyopathy and other cardiac diseases. The magnitude of these deficiencies is proportionate to the severity of disease, and decreasing levels of CoQ-10 are correlated with a decline in patient status.5 Data on the effective treatment of cardiomyopathy with CoQ-10 suggest that a myocardial deficiency of CoQ-10 may be one cause of cardiac dysfunction.

In 1957, Crane and coworkers isolated from mitochondrial lipids in bovine heart a compound they named “coenzyme Q,” which they proposed was a mediator of electron transport within the cellular respiratory chain.4 Subsequent structural determination revealed that the compound was identical to an earlier described quinone, named ubiquinone because of its widespread occurrence.5

In 1975, the International Union of Pure and Applied Chemistry and International Union of Biochemistry and Molecular Biology (IUPAC-IUB) Commission on Biochemical Nomenclature established this name as the “official” scientific designation for the compound, referring to its quinoid structure. This permitted easy reference to the partially reduced (ubiseniquinone) and fully reduced (ubiquinol) forms of the compound that reversibly interconvert via redox reactions. This property is key to ubiquinone’s roles in electron and proton transport in mitochondrial respiration coupled to synthesis of adenosine triphosphate (ATP) and its use as a powerful lipophilic antioxidant.5
CHEMISTRY

More commonly known as CoQ-10, ubiquinone is widely distributed in nature, where it is biosynthesized de novo in animals (including humans), plants, and microbes. Additionally, several homologues of CoQ-10 are known from various organisms. The homologues differ from CoQ-10 in the length of the lipophilic isoprenoid side chain. In birds, fish, and most mammals, only CoQ-10 itself is found. The major exception is a rodent that has the major CoQ-10 homologue called coenzyme Q-9 (the homologue of CoQ-10 containing 9 isoprene units) in addition to smaller amounts of CoQ-10. Rodent CoQ-10 biochemistry differs in that it also features shorter homologues of CoQ-10, including coenzyme Q-7 and coenzyme Q-8 in various tissues.

CoQ-10 biosynthesis in mammals is characterized by the convergence of 2 metabolic pathways. The quinone moiety is derived from tyrosine or phenylalanine, which are converted over several steps to 4-hydroxy-benzoate. The isoprenoid side chain is biosynthesized from acetly-coenzyme A (acetly-CoA) via the mevalonate pathway, through which cholesterol is produced as well. Acetly-CoA is converted via several enzymatic steps to farnesyl-pyrophosphate, the common precursor to both CoQ-10 and cholesterol. Farnesyl-pyrophosphate is then converted to decaprenyl-pyrophosphate (or solanesyl-pyrophosphate in rodents) and condenses with 4-hydroxy-benzoate, producing decaprenyl-4-hydroxy-benzoate, which results in CoQ-10 after several more biosynthetic steps.

As noted previously, CoQ-10 is a fundamental redox component of the respiratory chain within inner mitochondrial membranes. All respiratory chain enzymes except cytochrome oxidase require CoQ-10 as a coenzyme. As lipophilic, freely diffusible components of the mitochondrial membrane, both CoQ-10 and cytochrome-c mediate the electron transfer between complexes. This flow of electrons (from redox pairs with a more negative redox potential to pairs with a more positive redox potential) drives proton pumps that generate an electrochemical gradient (via the flow of protons from the mitochondrial matrix). The resulting "proton motive force" across the inner mitochondrial membrane is used to drive ATP synthase (complex V of the respiratory chain), whereby the protons are channeled back into the mitochondrial matrix where ATP, the "cellular currency of energy," is produced.

THERAPEUTIC APPLICATIONS

In one study, CoQ-10 status was determined to be inadequate in 40% of women and 24% of healthy people more than 30 years of age. An experimental study of aging in the rat has shown some decrease of mitochondrial CoQ-10 content in the heart, and even greater decrease in the liver and skeletal muscle. The authors reason that CoQ-10 administration may be beneficial in the elderly because of the aging body's increased demand for antioxidants.

Mitochondrial CoQ-10 levels are influenced by numerous factors, including dietary fat and physical exercise. A study conducted by Mataix et al. suggests monounsaturated dietary fats increase CoQ10 mitochondrial contents, whereas polyunsaturated fats decreased CoQ10 levels. Another study found that the highest mitochondrial CoQ-10 content was found in a diet supplemented with corn oil. A possible interpretation is that oil subjected to thermal treatment represents an oxidative insult, subsequently provoking a net decrease in endogenous CoQ. Only in the polyunsaturated fat diet were CoQ-10 levels elevated in response to aerobic performance.

New studies have shown that CoQ-10's unique biochemistry has diverse applications in all cellular membranes. One important function of CoQ-10 is in plasma membrane electron transport. CoQ-10 potentiates the activation of signaling protein kinases related to gene expression in cellular proliferation. In addition, CoQ-10 has recently been found to function as a co-antioxidant with tocopherol (within membranes) and ascorbate (both intracellularly and extracellularly, via CoQ-10's ability to maintain both of these compounds in their reduced states).

The ubiquinol/ubiquinone ratio in plasma has been proposed as a marker of oxidative stress. Oxidative stress has been defined as a disturbance in pro-oxidant/antioxidant balance, which is biased toward greater pro-oxidant activity. Pro-oxidant activity is alleged to be a factor in aging as well as in various pathological conditions. Patients who experience oxidative stress have more CoQ-10 than ubiquinol compared to healthy patients. CoQ-10 levels reach their peak in most tissues by the time a person reaches the age of 20 and then fall slowly thereafter. This decrease in CoQ-10 content during aging is consistent with the "free-radical theory of aging," as demonstrated by the inverse correlation between longevity and peroxide-producing potential in mammalian tissues. Disorders observed during the process of aging may relate to the diminished capacity of an organism to maintain adequate ubiquinol levels in relation to the necessity for protection from oxidative insult.

The role of the ubisemiquinone radical in respiratory chain redox cycling has raised the question of the possible role of this compound in the generation of oxygen radicals; that is, a pro-oxidant effect. An increasing body of evidence, however, refutes the assumption that free-radical generation is an inevitable side effect of respiration. Schnurr and colleagues have reported another type of pro-oxidant effect for CoQ-10 that involves 15-lipoxygenase in the biologically programmed degradation of mitochondria during the maturation of red blood cells.

PRECLINICAL STUDIES

Cardiovascular and Circulatory Functions

Hypertension. In stroke-prone, spontaneously hypertensive rats, CoQ10 treatment attenuated the blood pressure elevation, the degradation of membrane phospholipids, and the enhanced phospholipase A2 activity in the renal membrane. Researchers speculated that these effects were due to a renal membrane-stabilizing activity of CoQ10.

Ischemia-Reperfusion Injury. Several reports exist in the literature indicating a protective role of CoQ-10 against ischemia-reperfusion injury. A study was conducted in swine hearts to determine the mechanism of action by which CoQ-10 protects heart tissue. The results of the study demonstrated that pigs fed
CoQ-10 (5 mg/kg/d) for 30 days fared significantly better: they had less myocardial infarction and less creatine kinase release. The hearts of animals fed CoQ-10 had higher levels of CoQ-10, higher levels of the intracellular antioxidants ascorbate and thiol, and an increased amount of ubiquinon gene expression, all of which may contribute to the observed increased resistance to ischemic injury. Results of this study suggest that nutritional supplementation with CoQ-10 renders the heart resistant to ischemia-reperfusion injury, probably by reducing oxidative stress.

In addition to swine hearts, the effects of CoQ-10 on ischemia-reperfusion injury have also been studied in rat livers. Pentoxifylline (PTX) is a hemorrheologic drug that improves capillary blood flow by increasing erythrocyte flexibility and reducing blood viscosity. Portakal et al. investigated whether the addition of CoQ-10 to PTX treatment affects the outcome of laboratory-induced ischemia-reperfusion injury. Whereas PTX treatment alone did not cause beneficial effect in the measured outcome variables, the combination of CoQ-10 and PTX pretreatment proved useful. This combination prevented glutathione depletion and curbed the elevation of malondialdehyde, catalase, and superoxide dismutase typically seen in ischemia-reperfusion injury.

Thrombosis, Hemostasis, and Embolism. In a randomized, placebo-controlled study in female pigs, Serebranuy et al. found that CoQ-10 (100 mg twice a day for 20 days) decreased levels of eicosanoids and endothelin-1, a potent endothelium-derived vasoconstrictor. Abnormal hemostasis plays an important role in the pathogenesis of coronary artery disease, and free radicals have strong platelet proaggregatory properties. Dietary CoQ-10 supplementation was examined in experiments using swine (chosen for their hemostatic parameters, which are similar to those of humans). Serum levels more than doubled after 20 days of supplementation with 200 mg of oral CoQ-10. This was correlated with decreases in ADP-induced platelet aggregation, eicosanoid levels, and levels of endothelin-1. Researchers suggested that some of the reported clinical benefits with regard to cardiovascular morbidity and mortality of CoQ-10 supplementation may be due to improved hemostatic profile and a reduction in possible thrombotic and thromboembolic complications.

The effect of CoQ-10 was assessed on aortic lipoprotein lipid peroxidation and atherosclerosis in apolipoprotein-E−/− mice fed a high-fat diet. CoQ-10 treatment significantly decreased atherosclerotic lesions in the aortic root and descending aorta and decreased the absolute concentrations of hydroperoxides of cholesteryl esters and triacylglycerols.

Rabbits fed a diet rich in trans fatty acids were supplemented with 3 mg/kg/d of CoQ-10 in a randomized, single-blind, controlled trial. Intervention with CoQ-10 was associated with changes indicative of decreased oxidative damage. The aortic and coronary artery plaque sizes and the atherosclerosis scores of each were significantly lower in the CoQ-10 group versus placebo. Aortic and coronary plaque frequencies, as well as frequencies of ulceration, thrombosis, or hemorrhage and cracks and fissures, were also significantly lower in the CoQ-10 group. These and other markers from the study suggest that CoQ-10 can have a beneficial effect on the chemical composition of atheroma.

CLINICAL STUDIES
Cardiovascular and Circulatory Disorders
Cardioprotection. From a meta-analysis of the main placebo-controlled clinical trials on CoQ-10 (1986-1995), Soja and Mortensen concluded that scores for various parameters of cardiac function were significantly better for patients treated with CoQ-10 than for patients given placebo. An average 73% of patients treated with CoQ-10 displayed improved cardiac output (P<0.05), 76% (P<0.05) had increased stroke volume, cardiac index was improved in 87% (P<0.001), diastolic index in 88% (P<0.001), and ejection fraction in 92% (P<0.001).

Watson et al. reported no significant benefit from CoQ-10 in 30 men with congestive heart failure (aged 44 to 66 years) diagnosed with chronic left-ventricular dysfunction (echocardiography less than 35%) secondary to idiopathic or ischemic dilated cardiomyopathy. The randomized, double-blind, placebo-controlled, crossover trial found no difference of any significance after treatment with CoQ-10 compared to placebo in functional capacity, well-being (quality of life according to the Minnesota Living With Heart Failure questionnaire), cardiac volumes, or left-ventricular ejection fraction; nor were changes of any significance evident in the hemodynamic data. Watson et al. noted that both the dosage and duration of the therapy (33 mg orally 3 times daily for 3 months) were comparable to those used in other trials of CoQ-10. The patients had a history of chronic heart failure of 6 months to 6.25 years, left-ventricular dysfunction for 3 months or more, and were clinically stable on angiotensin-converting enzyme inhibitor. Daily medications taken concurrently with CoQ-10 during the trial by the vast majority of patients consisted of digoxin, nitrates and hydralazines, and frusemide. Watson et al. commented that restoring left ventricular ejection fraction did not improve therapy with CoQ-10. However, no adverse events occurred, no altered hematologic parameters or deleterious changes in renal or hepatic function were found, and the patients achieved plasma levels of CoQ-10 of about double their baseline readings.

Singh and Niazz examined the effect of CoQ-10 (Hydrosoluble Q-gel; Tishcon Corp, Westbury, NY) on serum alpha-lipoprotein in a randomized, double-blind, placebo-controlled trial in 35 patients diagnosed with acute coronary artery disease and a moderate elevation of alpha-lipoprotein. Alpha-lipoprotein is associated with both the occurrence and recurrence of cardiac death and myocardial infarction. The placebo group received a vitamin B-complex while the CoQ-10 group received a dose of 120 mg twice daily for the same 28 days. The results showed that, compared to placebo, there was a significant increase in the CoQ-10 group in levels of high-density lipoprotein (HDL) cholesterol and significant decreases in fasting blood glucose, malondialdehyde (MDA), diene conjugates, lipid peroxides, and especially alpha-lipoprotein (P<0.001), which dropped by 31.0%, versus 8.2% in the placebo group. LDL and total cholesterol showed no change. Adverse events, mostly nausea (36%), vomiting (24%), and hypotension in the first week of therapy (24%), occurred in 30 subjects in
the CoQ-10 group, compared to 13 subjects in the placebo group, and were assessed as mild.\(^2\)

Taggart and colleagues\(^2\) studied the effects of short-term supplementation of CoQ-10 on myocardial protection during cardioplegia in a double-blind, placebo-controlled study of patients having well-preserved ventricular function. The CoQ-10 treatment group received 2 oral doses of 300 mg, the first on the evening before and the second on the morning of the cardiopulmonary bypass operation. These researchers found no difference between treated and untreated groups with regard to biochemical markers of cardiac injury, and no cases of low cardiac output requiring inotropic support; however, preoperative blood tests revealed no difference in plasma CoQ-10 levels between treated and untreated groups. These researchers suggested that this was due to rapid uptake of exogenous CoQ-10 into plasma lipoproteins and subsequent concentration in liver, myocardium, and other sites, and that longer treatment durations led to a greater steady-state concentration of CoQ-10 in plasma. They also noted that their patient groups had relatively well-preserved ventricular function and short ischemic times. Taggart and colleagues concluded that patients whose myocardial function was the most impaired, with clear evidence of a deficiency in endogenous CoQ-10 such as those in heart failure or undergoing valve replacement, would benefit most from CoQ-10 supplementation.\(^3\)

Hofman-Bang et al.\(^4\) examined the effect of CoQ-10 in a double-blind, crossover, placebo-controlled study in which the treatment was an adjunct to conventional therapy. Patients were all diagnosed with stable chronic congestive heart failure. Thirteen of the patients were diagnosed at class II on the New York Heart Association (NYHA) functional scale, 60 at class III, and 6 at class IV. The vast majority were receiving treatments with diuretics, digitalis, and angiotensin-converting enzyme inhibitors. Hofman-Bang and colleagues reported that in their 3-month trial, compared to placebo, 100 mg/d of CoQ-10 (Pharmacia, Stockholm, Sweden) produced no significant differences in measurements of the ejection fraction, the primary endpoint of their study. However, CoQ-10 produced a significant increase (\(P<0.05\)) in ejection fraction during the volume-load test with legs up, as well as significant improvement (\(P<0.05\)) in maximum exercise tolerance. Also significant (\(P<0.05\)) was the decrease in the end of exercise score for leg fatigue and dyspnea, and the difference in the quality-of-life questionnaire total score versus placebo (\(P<0.05\)), in which life satisfaction and physical activity scores were significantly higher than those in the placebo group. No significant changes were found in blood specimens, and no patients were changed from their initial NYHA classification. An insignificant difference was found in the number of patients in each phase of the study who reported side effects, none of which could reasonably be ascribed to CoQ-10. The authors concluded that, though the changes were significant in quality of life and exercise capacity, these were still only slight improvements, and the clinical importance of these differences remained unclear.\(^5\)

Langsjoen et al.\(^6\) recorded the clinical outcomes of 424 cardiovascular disease patients who received CoQ-10 as an adjunct therapy over a period of 8 years. Doses averaged 242 mg/d (75 to 600 mg/d), and in many cases the goal was to reach a whole blood level of \(\geq 2.0\) mg/mL. An average whole blood level of 2.92 mg/mL was achieved in 287 subjects. Regardless of the different categories of patients, clinical responses were evaluated according to the NYHA functional scale. Compared to baseline readings, significant improvements were recorded in the majority in fatigue, chest pain, palpitations, and dyspnea, along with improvements in the NYHA functional scale according to classes of function; 247 subjects improved by 1 class; 120 subjects improved by 2 classes. The authors point out that, apart from 1 subject reporting transient nausea, there were no side effects from CoQ-10, and improvements were gradual and sustained.\(^7\) It is interesting to note that these researchers found that over time, absorption of CoQ-10 commercial products could be enhanced by chewing and swallowing a fat-containing food; for example, peanut butter.

Cardioplegia is the process by which cardiac function is temporarily arrested via hypothermia, medication, or electrical stimuli to reduce myocardial oxygen demand during cardiopulmonary bypass. Chen et al.\(^8\) reported that a double-blind trial of the effectiveness of oral CoQ-10 pretreatment (150 to 200 mg/d for 5 to 7 days, 1000 mg total) on myocardial preservation during cardioplegia revealed the following:

- Treated patients displayed better preservation of myocardial function, as demonstrated by a slightly decreased incidence of low cardiac output and wider pulse pressure.
- Treated patients' right and left ventricular myocardial structure was better preserved.
- No demonstrable benefit could be found regarding preservation of atrial myocardium.

Chen and coworkers noted that in both groups, atrial function was less well preserved because of the following:

- Topical cooling of the atrium was less effective because of its position during cardioplegia (maintenance of profound hypothermia is paramount in protecting myocardial tissue).
- Noncoronary collateral blood flow caused early washout of the cardioplegia solution.
- Cardioplegic solution was delivered differentially; all atrial regions received approximately half as much solution per gram of tissue as did the ventricles.

Chen et al.\(^9\) concluded that CoQ-10 helps preserve ventricular myocardial function during cardioplegic arrest, most likely via its effects on cellular energetics, membrane stability, and myocardial oxidative load.

Permanetter and colleagues\(^10\) conducted a placebo-controlled, double-blind, crossover study with CoQ-10 (33.3 mg given orally 3 times/day) in 25 chronic heart failure patients (aged 31 to 71 years) diagnosed with dilated cardiomyopathy. Four patients were symptom free at NYHA class I, 7 were at class II, and 15 were at class III. The 2 groups of patients were well-balanced except that 15 patients in group 2 were taking digitalis, compared to 8 patients in group 1. CoQ-10 was suspended in soya oil and provided in capsules (Zyma GmbH; Munich,
Germany). The other accompanying medications were diuretics, nifedipine, and nitrates. Results showed that while only 1 patient had to be excluded because of the need for a heart transplant, there were no significant differences between placebo and CoQ-10 in any measurements, either in the cardiothoracic ratio, maximum exercise capacity, exercise tolerance, echocardiography of the left ventricle, left ventricle ejection time, stroke volume index, or cardiac index. No side effects could be ascribed to CoQ-10, and function tests of liver and kidneys, blood count, and serum levels of electrolytes showed nothing out of the ordinary. The authors commented that 1 reason for the equivalent results might have been that other trials involved patients in worse condition than theirs.26

Judy et al recorded improved long-term survival for patients with NYHA class IV congestive heart failure who were treated with CoQ-10, when compared with a conventionally treated control group. Congestive heart-failure patients on CoQ-10 were also found to relapse when taken off this treatment. Judy et al studied the short-term effect of CoQ-10 (100 mg/d for 90 days) in 14 NYHA class IV patients, aged 52 to 76 years, who had been diagnosed with cardiac failure. The randomized, double-blind, placebo-controlled, crossover study found that patient response to CoQ-10 varied, with some patients showing improvements in cardiac function after 30 to 45 days and others showing improvements after 60 to 90 days. CoQ-10 treatment for 90 days resulted in patients’ cardiac index attaining normal levels; however, left ventricular end diastolic volume index and ejection fraction showed no normalization, nor was there improvement after a year of treatment with CoQ-10 in these patients. Judy et al concluded that their results supported previous findings with CoQ-10 in congestive heart failure, adding that if CoQ-10 treatment is stopped, a gradual decrease in cardiac function ensues at variable rates from 1 patient to the next. Patients who showed declining cardiac function during the placebo phase showed improvement when they were treated again with CoQ-10 after 180 days.

Poggesi and colleagues conducted a double-blind, placebo-controlled, crossover study of the effects of CoQ-10 (100 mg/d orally for 60 days) in patients with dilative cardiomyopathy. Significant improvement in left ventricular systolic function was noted following CoQ-10 treatment. After a 30-day washout period, effects returned to baseline levels, indicating that functional improvement was linked to drug administration and, therefore, to serum and myocardial levels of CoQ-10. Since the improved function was seen in both ischemic and idiopathic cardiomyopathies, the therapeutic efficacy of CoQ-10 was independent of coronary blood flow. These researchers concluded that oral CoQ-10 is a safe and effective treatment for dilatative cardiomyopathies of different etiology and that this efficacy may be due to CoQ-10’s supportive and enhancing effect on myocardial tissue energetics.27

Serra et al reported beneficial results from CoQ-10 (60 mg/d orally for 28 days) added to “usual treatment” in a randomized, double-blind, crossover, placebo-controlled study of 20 chronic ischemic heart disease outpatients (aged 44 to 70 years, with 15 in NYHA class II and 5 in class III) diagnosed with symptoms of stable-effort angina, sinus rhythm, and mild or moderate heart failure. The condition of 13 of the patients resulted from chronic artery disease; the condition of the remainder was from left ventricular hypertrophy resulting from left ventricular hypertension. Study results showed that, compared to placebo, CoQ-10 produced a significant improvement in heart failure scores, cardiothoracic ratio, number of angina attacks per week, stroke volume, cardiac output, exercise duration (26 minutes versus 3 minutes for placebo, P < 0.01) and endpoint, workload, and a significant reduction in the number of nitrate tablets consumed per week (P < 0.01). At the end of the treatment period, 4 of the 5 patients in NYHA class III were diagnosed class II, and 4 of the 15 NYHA class II patients improved to NYHA class I. Side effects from CoQ-10 were insignificant, with 3 patients reporting slight gastralgia.27

A double-blind, double-crossover, placebo-controlled trial involving 19 patients with chronic, stable, moderately advanced myocardial disease found that treatment with oral CoQ-10 (33 mg 3 times daily for 24 weeks) resulted in improvements in myocardial function that were positively correlated with increasing blood levels of CoQ-10, demonstrating that CoQ-10 deficiencies in humans are treatable through supplementation. A decline in cardiac function was correlated with a decrease in CoQ-10 levels when patients were moved to placebo, indicating that the causes of the initial deficiency were not affected. Clinical improvement was demonstrated by tolerance of increased activity in 95% of the patients; some of the physical improvements were reported to be remarkable. No adverse reactions to the drug were reported.27

These researchers’ theorized that the remarkable clinical improvement in the patients’ cardiomyopathy resulted from improved bioenergetics, which support improved cardiac function of impaired but still viable myocardial cells. The reappearance of symptoms of dysfunction when CoQ-10 was replaced by placebo suggested to these researchers that CoQ-10 deficiency might be a major cause of cardiomyopathy and that lifetime therapy with CoQ-10 may be mandatory for the cardiac patient.

Hypertension. Singh et al studied the effect of 60 mg of CoQ-10 (Q-gel hydrosoluble CoQ-10 Softsules; Tishcon Corp, Westbury, NY) given twice daily for 8 weeks in 64 coronary artery disease patients being treated with antihypertensive medication for more than 1 year to test the hypothesis that CoQ-10 could decrease oxidative stress and blood pressure in these patients. The randomized, double-blind trial was performed as part of a main trial of CoQ-10 in acute coronary artery disease (previously published28). The control group received a B-vitamin complex in capsules. When compared to the placebo group, a significant decrease was found in the men treated with CoQ-10 in diastolic and systolic blood pressure, waist-to-hip ratio, and heart rate. Fasting triglyceride levels, 2-hour plasma insulin, fasting insulin, and plasma glucose levels all showed a significant decrease in the CoQ-10-treated patients compared to placebo. HDL cholesterol levels were significantly increased compared to the control group, and significantly fewer patients treated with
CoQ-10 used sublingual trinitrate every day, experienced angina pectoris, or used diltiazem, enalapril malate, metoprolol, or nitrate compared to the placebo group. Indicators of free radical stress (diene conjugates, lipid peroxides, and MDA) also decreased significantly in the CoQ-10 group, and this group’s levels of vitamins C, E, and beta carotene showed a significant increase. The B-vitamin control group showed a significant increase only in beta carotene and vitamin C. CoQ-10 treatment resulting in decreased blood pressure has previously been reported by others. 8

A 12-week, randomized, double-blind, placebo-controlled trial with twice daily oral administration of 60 mg CoQ-10 resulted in a mean reduction in systolic blood pressure of 17.8 ± 7.3 mm Hg. All subjects discontinued any existing antihypertensive therapy before participation in the study. Analysis of individual patient data revealed that 55% of patients in the CoQ-10 treatment group achieved a reduction in systolic blood pressure of >4 mm Hg, while 45% of patients were nonresponders. In the subset of patients who were responders, the average reduction in systolic blood pressure was 25.9 ± 6.4 mm Hg. 9

Thrombosis, Hemostasis, and Embolism. Serebruany et al.7 in an open-label study, treated 12 normal volunteers with oral CoQ-10 (200 mg/d). At day 20 of treatment, serum levels of CoQ-10 had increased from a mean of 0.6 mg/mL to 1.8 mg/mL. This was correlated with a decrease in platelet size and platelet vitronectin receptor expression. Platelet size was positively correlated with platelet activity, and vitronectin is a serum glycoprotein that promotes cell adhesion, among other processes. The researchers speculated that some of the known clinical benefits of CoQ-10 for cardiovascular disorders were partially due to inhibition of platelet activity.

In an open-label study,7 CoQ-10 decreased platelet aggregation and also decreased platelet size in healthy volunteers (aged 24 to 43 years) of both sexes who were given 100 mg CoQ-10 twice a day for 20 days. In an 8-week open-label study,20 CoQ-10 decreased blood viscosity in ischemic heart disease patients (mean age 49 ± 16 years) given 20 mg CoQ-10 3 times daily. CoQ-10 decreased blood viscosity without affecting the patients’ hematocrit or fibrinogen levels.

In an 8-week study,20 Kato et al found that blood viscosity (expressed as yield shear stress) was reduced in their 12 subjects, while hematocrit (red blood cell count) and fibrinogen levels were not affected. Since hematocrit and fibrinogen levels were not affected by CoQ-10 treatment, these researchers speculated that the effects of CoQ-10 on membrane properties were the cause of the observed effect by diminishing erythrocyte aggregation and improving erythrocyte deformability.

Congestive Heart Failure. In a randomized, double-blind, controlled trial, the effect of coenzyme Q-10 was assessed in 55 patients with congestive heart failure. Although the mean serum concentration of CoQ-10 increased in patients who received active treatment, the ejection fraction, peak oxygen consumption, and exercise duration remained unchanged in both CoQ-10 and placebo groups. Subjective parameters were not monitored in the study.20

DOSAGE

Most clinical studies demonstrating the therapeutic efficacy of oral CoQ-10 in the treatment of cardiovascular disorders have employed doses in the range of 100 to 240 mg/d. However, oral dosages as low as 60 mg/d result in greater than baseline serum concentrations and can improve certain hemodynamic parameters.20,21 Research indicates that therapeutic blood levels of CoQ-10 should be at least 2.5 mg/mL to elicit a biosensitive result.3

Effective treatment regimens for mitochondrial encephalomyopathies have employed oral doses of CoQ-10 in the range of 150 to 300 mg/d for extended periods of time (several months to several years). For these disorders, the literature suggests that shorter treatment periods are less likely to be beneficial.20,21

Oral doses of CoQ-10 at 60 mg/day have been associated with improvement of some immunological parameters in cancer patients.19 However, treatment protocols displaying results on tumor reduction and suppression used oral doses of CoQ-10 at 300 to 400 mg/d, which were well tolerated and free of side effects.19,20

The optimum protective dose against adriamycin-induced cardiotoxicity was 10 mg/kg/d given orally in mice.7

Neurodegenerative diseases that feature mitochondrial respiratory chain defects such as Huntington’s disease and Parkinson’s disease have been treated with high oral doses of CoQ-10: 600 to 1200 mg/d for Huntington’s disease treatment protocols22 and 200 to 800 mg/d for treatment of Parkinson’s disease.6

Moderate variability in the absorption of CoQ-10 has been observed, with some individuals requiring 2 or 3 times the amount needed by the average subject to attain the same blood level. Krone et al observed several patients suspected of having Candida albicans overgrowth who did not respond as expected to CoQ-10 supplementation. An in vitro pilot study was conducted that suggested CoQ-10 was biologically functional in this yeast. The authors theorize that C. albicans overgrowth in the intestinal tract may lessen the amount of CoQ-10 available to the host, suggesting that the fungus uses the nutrient for its own mitochondrial respiratory chain.

SAFETY PROFILE

Few adverse effects of CoQ-10 have been reported in the literature, and these are invariably of such a mild nature that they do not require cessation of treatment or medical intervention. As an example, an Italian multicenter, open-label, noncomparative, preliminary, postmarketing drug surveillance study was conducted on the safety and efficacy of oral CoQ-10 in the treatment of heart failure. Subjects received either 100 mg/d (78%) or 50 to 150 mg/d (22%). Following a 90-day treatment period, the incidence of side effects reported was no more than 7%. Ten adverse reactions were reported by 8 of 1113 patients studied, with only 5 of the reactions considered attributable to the treatment.23 A subsequent drug surveillance study of all the participants in the trial reported a 1.5% incidence of side effects: 38 adverse reactions were reported by 36 of 2664 patients, with only 22 of the reactions considered attributable to the treatment.24
Contraindications
Because CoQ-10 affects the metabolism of the quinone antioxidant vitamin E, and cancer agent Adriamycin (by increasing the concentrations of a putatively toxic Adriamycin metabolite), CoQ-10 treatment should not be undertaken during chemotherapy with this agent.6 However, the use of CoQ-10 after cessation of chemotherapy has been reported as beneficial.6

Drug Interactions
Patients with hypertension receiving antihypertensive drugs may show decreased blood pressure, decreased oxidative stress, and a decreased insulin response, along with increased levels of antioxidant vitamins when antihypertensive drugs are taken concomitantly with CoQ-10. Patients may also show a decreased intake of medications and report less angina pectoris.5

Lovastatin is clinically used to treat hypercholesterolemia. It successfully lowers cholesterol levels through the inhibition of HMG-CoA reductase, an enzyme in the mevalonate pathway involved in the biosynthesis of cholesterol from acetyl-CoA. Since inhibition of this enzyme also inhibits the biosynthesis of CoQ-10, it was hypothesized that the clinical use of lovastatin to reduce the risk of cardiac disease could constitute a new risk of cardiac disease, because CoQ-10 has been demonstrated to be indispensable for cardiac function.32

Hypercholesterolemic noninsulin-dependent diabetic patients treated with simvastatin or pravastatin showed lower levels of CoQ-10 following treatment and significantly increased levels following CoQ-10 supplementation (30 mg/d for 6 months). It was suggested51 that a significant decrease in cardiothoracic ratios in 14 of 17 patients treated with CoQ-10 and HMG-CoA reductase inhibitors may have been associated with an undiagnosed diabetic cardiomyopathy that was ameliorated by CoQ-10. However, whether mitochondrial dysfunction from treatment with statins can be associated with low-serum concentrations of CoQ-10 is uncertain.48 Similarly, the cholesterol-lowering drug gemfibrozil is reported to decrease serum CoQ-10 levels in hyperlipidemic men.42 In a 6-month clinical investigation, simvastatin (20 mg/d) lowered total serum CoQ-10 levels in hypercholesterolemic patients by 25% compared to untreated healthy controls. However, muscle CoQ-10 concentrations showed no appreciable difference compared to healthy controls, and the antioxidant capacity of LDL was not significantly different from baseline.20 A double-blind, placebo-controlled crossover study of lovastatin (60 mg/d) combined with CoQ-10 supplementation (180 mg/d) also found no significant improvement in the antioxidative capacity of LDL, as measured by copper-mediated oxidation.37

A new development in the field of cholesterol management is the use of the fungal product squalestatin 1 as an inhibitor of cholesterol synthesis. This compound is a potent, specific inhibitor of squalene synthetase. Because this enzyme occurs below the branch point in the mevalonate pathway leading to CoQ-10, cholesterol synthesis is inhibited without affecting CoQ-10 or dolichol biosynthesis. Moreover, it has recently been reported that squalestatin 1 treatment can increase CoQ-10 levels 3- to 4-fold, presumably due to pooling of farnesyl pyrophosphate, the common precursor of cholesterol, dolichol, and CoQ-10.5

A decreased international normalization ratio has been reported in several elderly patients following their addition of CoQ-10 to treatment regimens with warfarin.57 In 2 cases, the dose of CoQ-10 was known (30 mg/d). Correcting the problem may require temporarily increasing the dose of warfarin and ceasing supplementation with CoQ-10. CoQ-10 is structurally related to menaquinone (vitamin K,) and may have procoagulant effects.44 The interaction may be the result of CoQ-10 antagonizing vitamin K,, though this has yet to be shown in vivo.60

Some evidence suggests that in male power athletes (aged 24 to 34 years) who abuse anabolic androgenic steroids (intramuscularly or orally), serum concentrations of endogenous CoQ-10 can become significantly increased (by 68%).58

In mice, oral administration of CoQ-10 (10 mg/kg/d for 3 days), as a membrane stabilizer and antioxidant for prevention of cardiotoxicity before Adriamycin chemotherapy, was associated with significantly elevated levels of an Adriamycin metabolite in liver, heart, and kidney. Elevated levels of this metabolite are associated with decreased survival in murine models.60

Pregnancy and Lactation
No contraindications appear in the literature concerning the use of CoQ-10 during pregnancy and lactation. However, because of its hemodynamic, bioenergetic, and immunoennergic effects, caution should be exercised when CoQ-10 is used during pregnancy.

Side Effects
During an open study31 investigating the effectiveness of high oral doses of CoQ-10 (600 to 1200 mg/d) in the treatment of Huntington’s disease, 6 of 10 patients reported the following adverse experiences, which were rated as mild and only possibly due to CoQ-10: headache, heartburn, fatigue, and an increase in the involuntary movements characteristics of the disorder. A second study in patients with Huntington’s disease53 reported an increased frequency of stomach upset with supplementation of 300 mg of CoQ-10 twice a day.

Similarly, a study of CoQ-10 in the treatment of Parkinson’s disease39 reported “mild, transient changes in the urine” at the highest oral dose tested: 200 mg given 4 times/day.

When Singh et al47 investigated their hypothesis that CoQ-10 could decrease oxidative stress and blood pressure in patients receiving antihypertensive medication, adverse effects were, in most instances, more frequently reported in the CoQ-10 group than in the control group: abdominal discomfort (2 in the CoQ-10 group, compared to 1 in the control group), headache (1, compared to 1), nausea (6, compared to 3), and vomiting (2, compared to 1).

Special Precautions
Patients undergoing chemotherapy with doxorubicin should not take CoQ-10 concurrently due to its ability to increase levels of a potentially toxic doxorubicin metabolite.60 CoQ-10 has
been used to treat the oxidative damage-induced cardiotoxicity caused by many antineoplastic drugs. Concurrent use of CoQ-10 and epirubicin during breast cancer chemotherapy is associated with an alleviation of the cardiac dysfunction seen when epirubicin is used alone. CoQ-10 also successfully treats doxorubicin cardiotoxicity when administered after discontinuation of chemotherapy. Simultaneous use of CoQ-10 and doxorubicin, however, may be contraindicated. Tissue concentrations of doxorubicin and its major metabolite (aglycone 1) were examined in mice pretreated with CoQ-10. In the CoQ-10-pretreated group, the concentrations of aglycone 1 in the heart, liver, and kidney (at 1 hour and 3 hours) were significantly higher than in the control group. Elevated levels of this doxorubicin metabolite are associated with decreased survival in murine models; therefore, clinical application of CoQ-10 concomitant with antitumor drugs (especially doxorubicin) requires special caution.

Animal studies indicate that treatment of human small-cell lung cancer with gamma radiotherapy could be compromised by high doses of CoQ-10. A significant dose-dependent decrease in tumor responsiveness to radiation was found from oral administration of CoQ-10 to tumor-transplanted mice at doses equivalent to 40 mg/kg given orally. This decreased response was borderline at the equivalent of 20 mg/kg. However, inhibited tumor susceptibility to radiation was not found at the equivalent of 10 mg/kg.

No documented reports of overdosage from CoQ-10 appear in the medical literature.

References


