

Supplemental ubiquinol in patients with advanced congestive heart failure

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Abstract. Patients with CHF, NYHA class IV, often fail to achieve adequate plasma CoQ₁₀ levels on supplemental ubiquinone at dosages up to 900 mg/day. These patients often have plasma total CoQ₁₀ levels of less than 2.5 $\mu\text{g/ml}$ and have limited clinical improvement. It is postulated that the intestinal edema in these critically ill patients may impair CoQ₁₀ absorption. We identified seven patients with advanced CHF (mean EF 22%) with sub-therapeutic plasma CoQ₁₀ levels with mean level of 1.6 $\mu\text{g/ml}$ on an average dose of 450 mg of ubiquinone daily (150–600 mg/day). All seven of these patients were changed to an average of 580 mg/day of ubiquinol (450–900 mg/day) with follow-up plasma CoQ₁₀ levels, clinical status, and EF measurements by echocardiography. Mean plasma CoQ₁₀ levels increased from 1.6 $\mu\text{g/ml}$ (0.9–2.0 $\mu\text{g/ml}$) up to 6.5 $\mu\text{g/ml}$ (2.6–9.3 $\mu\text{g/ml}$). Mean EF improved from 22% (10–35%) up to 39% (10–60%) and clinical improvement has been remarkable with NYHA class improving from a mean of IV to a mean of II (I to III). Ubiquinol has dramatically improved absorption in patients with severe heart failure and the improvement in plasma CoQ₁₀ levels is correlated with both clinical improvement and improvement in measurement of left ventricular function.

Keywords: Class IV congestive heart failure, end stage CHF, CoQ₁₀, coenzyme Q₁₀, ubiquinone, ubiquinol, vitamin E, cholesterol

1. Introduction

Since the first Japanese trials of supplemental coenzyme Q₁₀ (CoQ₁₀) in the mid and late 1960's [27,28], it has become apparent that the CoQ₁₀ molecule is inherently poorly absorbed. Some improvements in CoQ₁₀ absorption were documented with a variety of innovative formulations and all CoQ₁₀ supplements are better absorbed with meals. The latest advance in supplemental CoQ₁₀ is a stabilized reduced ubiquinol product developed by Kaneka Corporation of Japan and is available as an over-the-counter supplement under the trade name Kaneka QHTM (www.kanekaQH.com) [5].

The importance of absorption relates to the importance of plasma CoQ₁₀ levels attained in clinical trials, first in heart failure and later in neurodegenerative disease. In the 1970's and early 1980's patients with heart failure were noted to have on average lower plasma CoQ₁₀ levels and that the degree of CoQ₁₀ deficiency in blood and heart muscle correlated with the degree of heart failure. Early supplemental strategy focused on returning plasma CoQ₁₀ levels to a normal range, for example, increasing plasma CoQ₁₀ from $0.6 \pm 0.2 \mu\text{g/ml}$ to $1.0 \pm 0.2 \mu\text{g/ml}$. This strategy was analogous to the highly effective treatment of thiamine (vitamin B1) deficient heart failure (Beri-Beri) with supplemental vitamin B1 [13].

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In the course of a six year study of supplemental CoQ₁₀ in 126 patients with heart failure, it became clear that this initial strategy of normalizing plasma CoQ₁₀ status was not effective [11]. Only patients with plasma CoQ₁₀ levels > 2.5 µg/ml showed significant clinical and echocardiographic improvement in heart failure. Due to individual variation in patient's ability to absorb CoQ₁₀ we began to adopt a flexible dosing schedule whereby CoQ₁₀ dosage was increased as necessary to attain plasma CoQ₁₀ level of > 2.5 µg/ml. In many cases this required 600 mg CoQ₁₀ per day. Of a total of 23 randomized controlled trials of supplemental CoQ₁₀ in congestive heart failure from 1972 to 2006 [1–3,6–10,12–26], 20 found significant benefit while only three trials failed to show benefit. One study by Permanetter et al. failed to measure CoQ₁₀ levels [18] and the other two controlled studies demonstrated sub-therapeutic plasma CoQ₁₀ levels on therapy. The study by Watson et al. demonstrated a mean plasma CoQ₁₀ level of only 1.7 µg/ml in the treatment group with only two of 30 patients having a level greater than 2.0 µg/ml [26]. Finally, the trial by Khatta et al. demonstrated a mean plasma CoQ₁₀ level of 2.2 ± 1.2 µg/ml indicating that some patients on treatment had levels as low as 1.0 µg/ml. [9] The two most recent controlled trials by Belardinelli et al. showed significant benefit with treatment levels of 3.3 µg/ml and 3.6 µg/ml on 300 mg CoQ₁₀ per day [1,2].

Our experience over the past 25 years identified a subset of end-stage NYHA Class IV heart failure patients who had remarkably poor CoQ₁₀ absorption with low plasma CoQ₁₀ levels on up to 900 mg/day of CoQ₁₀. Preliminary data on a new stabilized ubiquinol formulation by Kaneka Corporation of Japan indicated significantly improved absorption as compared to any other CoQ₁₀ supplement, all of which are in the oxidized ubiquinone state. It was our purpose to see if ubiquinol could give better plasma CoQ₁₀ levels in these critically ill patients and, if so, if this would be associated with any clinical benefit.

2. Materials and methods

2.1. Study design, selection of participants and inclusion criteria

From June 2006 through May of 2007, seven consecutive patients who had worsening NYHA Class IV congestive heart failure on maximal medical therapy in addition to supplemental ubiquinone with sub-therapeutic plasma CoQ₁₀ levels (defined as < 2.5 µg/ml) were enrolled in an open study to assess the effect, if any, of changing their ubiquinone supplementation to ubiquinol. Patients were recruited from our existing cardiology practice over a period of 12 months. The seven patients in this study had a mean duration of CHF of 10 years (range 3 to 16 years) and were on ubiquinone in addition to conventional medical therapy for the same length of time. We excluded one patient with NYHA class IV heart failure whose plasma CoQ₁₀ was considered therapeutic at 6.9 µg/ml on 900 mg/day of ubiquinone. Her case is considered separately in the discussion section. Patients with brief decompensation into NYHA class IV heart failure who improved to class III, or better, after adjustment of conventional treatment were also excluded. In other words, we included only end-stage CHF patients, who were worsening despite maximal medical therapy, high dose ubiquinone and biventricular pacing when appropriate. All seven patients had sub-therapeutic plasma CoQ₁₀ levels, mean of 1.6 µg/ml, range 0.9 µg/ml to 2.0 µg/ml, on ubiquinone at mean daily dose of 450 mg/day, range 150 mg to 600 mg/day. Conventional therapy, including digitalis, diuretics, potassium, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta blockers, nitrates, antiarrhythmics and coumadin were either left the same or adjusted according to changing clinical status. All seven patients were changed from ubiquinone to ubiquinol in hopes of improving their rapidly deteriorating condition.

2.2. Analytical procedures

The analysis of reduced and oxidized forms of coenzyme Q₁₀ (CoQ₁₀) is based on previously published method [29].

2.2.1. Chemicals and reagents

Coenzyme Q₁₀ working standard was obtained in both oxidized (CoQ₁₀ or ubiquinone) and reduced (H₂CoQ₁₀ or ubiquinol) forms from Kaneka Corporation, Osaka, Japan. Vitamin E standard was purchased from Sigma-Aldrich, St. Louis, Missouri. Free cholesterol, cholesteryl linolenate, arachidonate, linoleate and oleate standards were obtained from Dr. Yorihiro Yamamoto's laboratory of University of Tokyo, Japan. HPLC grade methanol, 2-propanol, water and sodium perchlorate monohydrate were purchased from Fisher Scientific, Pittsburgh, PA.

2.2.2. Apparatus

The HPLC-UV-EC system is Shiseido Nanospace SI-2 semimicrocolumn system with Shiseido SS420 Interface and Data Processor/System Controller Integrated Software EZChrom Elite. The system is equipped with a 4-Flow Channel Degasser made by ERC, Inc. Model #L-761, two Shiseido inert pumps Model #3001, a cooled Shiseido Autosampler Model #3023, Shiseido High Pressure 6-way Single Switching Valve Model #3011, Shiseido Valve Communication Board Model #3107, Shiseido Column Oven Model #3004, Shiseido Ultraviolet-Visible Detector Model #3002 and Shiseido Electrochemical Detector Model #3005.

The isocratic HPLC system uses the following four columns:

1. CoQ₁₀ Concentrating HPLC Column (kept at room temperature): SupelcoSil™ LC-8, 3.3 cm × 4.6 mm, 3 μm.

The following three columns are kept at 40°C in column oven:

2. Guard HPLC column: SupelcoSil™ ABZ + PLUS, 3.3 cm × 4.6 mm, 3 μm.
3. CoQ₁₀ analytical HPLC column: SupelcoSil™ LC-8, 25 cm × 4.6 mm, 5 μm.
4. CoQ₁₀ Reduction Column: SHISEIDO RC-10, 30 mm × 4.0 mm.

2.2.3. Specimen collection and sample preparation

Minimum of 2 ml venous blood is drawn in green top sodium heparin vacutainer tube. Blood is centrifuged immediately to separate plasma. Fifty microliters of the plasma is pipetted into a 1.5ml labeled polypropylene microcentrifuge tube and the remaining plasma is pipetted into a second, amber-colored polypropylene tube to serve as reserve plasma for possible repeat analysis. Both tubes are frozen immediately at -80°C. For extraction, 950 μl of cold 2-propanol is added to the microcentrifuge tube with 50 μl of the frozen plasma, this is vortexed for 1 minute and promptly centrifuged at 12,000 rpm at 4°C for 3 minutes. The supernatant is immediately pipetted into autosampler tube and 40 μl is injected into the HPLC system. The autosampler is kept at 4°C.

2.2.4. HPLC analysis conditions

During the first two minutes of the analysis, the switching valve is in position "A" and the sample is first picked up by mobile phase I which is 50 mM sodium perchlorate in methanol/water (95/5, v/v) and this runs for 2 minutes with a flow rate of 400 ul/min through a pre-column which traps fat soluble compounds from the plasma extract and allows water-soluble compounds to proceed to waste. The switching valve then switches to mobile phase II which is 50 mM sodium perchlorate in methanol/2-propanol (90/10, v/v)

and this runs with a flow rate of 800 ul/min for 26 minutes through three columns located in a column oven kept at 40°C. The first column is a guard column, the second column is a separation analytical column which separates the reduced and oxidized CoQ₁₀ and the third column reduces the oxidized CoQ₁₀ so that it can be detected by ECD in oxidation mode. The sample then goes through the UV detector set at 210 nm for detection of free cholesterol, cholesteryl linolenate, arachidonate, linoleate and oleate. Finally, the sample passes through the ECD set at 600 mV for detection of Vitamin E (alpha tocopherol), and the separated reduced and oxidized CoQ₁₀ both of which are now in the reduced, ubiquinol state. During the last two minutes of the analysis the switching valve is back in the "A" position, running mobile phase I at flow rate of 400ul/min.

3. Case Studies

3.1. Case #1

The patient is a 66-year-old male with ischemic heart disease, which began with a myocardial infarction in 1989. On initial visit to our clinic December 2003 he had a 35% ejection fraction (EF). The patient continued to do poorly and despite two coronary stents, a biventricular implantable cardiac defibrillator and maximal medical therapy, including supplemental CoQ₁₀ at 450 mg/day, continued to worsen and by June 2006 had class IV symptoms and a 15% EF. He was requiring hospitalization every two to three weeks for inotropes, diuretics and repeat thoracentesis for large pleural effusions. At this time his plasma CoQ₁₀ level was 2.0 µg/ml (CoQ₁₀ to cholesterol ratio was 0.5 µmol/mmol) on 450 mg/day of ubiquinone. He was switched over to ubiquinol at 450 mg/day and by September 2006, his plasma CoQ₁₀ level had improved dramatically up to 7.8 µg/mL (CoQ₁₀/cholesterol ratio 1.7 µmol/mmol) with an improvement in his ejection fraction up to 35%. After eight months the patient increased his ubiquinol to 900 mg/day on his own and continued to improve. By February 2008 his ejection fraction was up to 60% and his clinical status was dramatically improved to NYHA class I status and plasma CoQ₁₀ level increased further to 9.3 µg/ml (CoQ₁₀ to cholesterol ratio was 2.8 µmol/mmol). LVEDD (left ventricular diastolic dimension) decreased from 7.4 cm to 5.8 cm with an associated improvement in the degree of mitral regurgitation.

3.2. Case #2

The patient was a 78 year old Caucasian female with critical aortic stenosis. In July 2000, the patient underwent aortic valve replacement with a tissue-type valve which unfortunately gradually restenosed and by March 2007 the patient was in NYHA class IV CHF with a severely stenotic prosthetic aortic valve and a 35% EF. In addition to conventional medical therapy the patient was on 600 mg/day of ubiquinone with plasma CoQ₁₀ level 0.9 µg/ml and CoQ₁₀/cholesterol ratio 0.3 µmol/mmol. The patient was changed to ubiquinol at 450 mg/day and within two months plasma CoQ₁₀ level increased to 2.6 µg/ml, CoQ₁₀/cholesterol ratio 0.6 µmol/mmol. Clinical status improved to NYHA class III and EF 50%. Unfortunately due to mental deterioration from cerebrovascular disease the patient stopped her CoQ₁₀ and within one month her plasma CoQ₁₀ level dropped to 1.5 µg/ml, CoQ₁₀/cholesterol ratio 0.4 µmol/mmol, with worsening CHF and a 30% EF. The LVEDD changed slightly from 4.7 cm to 4.4 cm over the three month course of supplemental ubiquinol treatment. She died of heart failure three months later.

3.3. Case #3

The patient is a 58 year old Caucasian female with ischemic cardiomyopathy, which began as a large anterior wall infarct in 1999 despite normal coronary anatomy. The patient's ejection fraction at that time was 18%. On standard medical therapy and ubiquinone at 150 mg/day she remained in stable NYHA class II status with a 25% EF up until decompensation in December 2006. By January 2007 she was in class IV CHF with a 10% EF and plasma CoQ₁₀ level 1.5 µg/ml with CoQ₁₀/cholesterol ratio 0.2 µmol/mmol. The patient was changed initially to ubiquinol 150 mg/day which increased plasma CoQ₁₀ level to 3.5 µg/ml, CoQ₁₀/cholesterol ratio 0.6 µmol/mmol after one month. Ubiquinol was then increased to 450 mg/day and by May 2007, her clinical status improved to NYHA class II with EF 25% and plasma CoQ₁₀ level 8.9 µg/ml with CoQ₁₀/cholesterol ratio 1.4 µmol/mmol. The patient returned to work and was stable up until she came down with influenza in January 2008 with associated decompensation to NYHA class IV CHF, a decrease in plasma CoQ₁₀ level to 5.5 µg/ml and a drop in EF back to 10%. This required hospitalization and placement of a biventricular ICD. As of February 2008, she is in NYHA class III status. Her LVEDD remained stable at 7.8 cm with moderate mitral regurgitation for the first 12 months of supplemental ubiquinol and then increased to 8.3 cm after the influenza.

3.4. Case #4

The patient is a 75 year old Caucasian male with a nine year history of hypertensive heart disease with left ventricular hypertrophy, diastolic dysfunction, chronic atrial fibrillation and a 55% EF. Despite good blood pressure control the patient deteriorated to NYHA class IV congestive heart failure and by March 2007 had a 35% EF with plasma CoQ₁₀ level 1.8 µg/ml, CoQ₁₀/cholesterol ratio 0.5 µmol/mmol on 300 mg/day of ubiquinone. The ubiquinone was increased to 600 mg/day with no clinical benefit and no improvement in plasma CoQ₁₀ level at 1.7 µg/ml, CoQ₁₀/cholesterol ratio 0.4 µmol/mmol. In May 2007 the patient was changed to ubiquinol at 450 mg/day and after one month plasma CoQ₁₀ level increased to 2.9 µg/ml, CoQ₁₀/cholesterol ratio 0.7 µmol/mmol with NYHA class II status, 40% EF. Ubiquinol was increased to 600 mg/day and by July 2007 plasma CoQ₁₀ level was 5.9 µg/ml, CoQ₁₀/cholesterol ratio 1.3 µmol/mmol. In September 2007 this patient's CoQ₁₀ level was 5.1 µg/ml and CoQ₁₀/cholesterol ratio 1.2 µmol/mmol and his clinical status was NYHA class I with a 50% EF. On his most recent visit, January 2008 he remains well on 600 mg/day ubiquinol with NYHA class I status and 60% EF. LVEDD remained unchanged at 5.5 cm during ubiquinol treatment.

3.5. Case #5

The patient is a 67 year old Caucasian male with ischemic cardiomyopathy with myocardial infarction and bypass graft surgery in 1991. This left him with about a 40% ejection fraction when we first evaluated the patient in February of 1996. The patient remained stable in NYHA class II on standard medical therapy and ubiquinone at 300 mg/day up until gradual deterioration to NYHA class III CHF in March 2007 with EF 30% and worsening diastolic dysfunction. Plasma CoQ₁₀ level was 2.6 µg/ml and CoQ₁₀/cholesterol ratio 0.4 µmol/mmol. The patient further worsened to class IV CHF and, despite increasing ubiquinone to 450 mg/day, his plasma CoQ₁₀ level declined to 1.5 µg/ml with CoQ₁₀/cholesterol ratio 0.3 µmol/mmol by April 2007. The patient was then changed to ubiquinol at 450 mg/day and after two months his clinical status improved to class II, EF increased to 50% and plasma CoQ₁₀ level increased to 4.4 µg/ml with CoQ₁₀/cholesterol ratio 0.9 µmol/mmol. By February 2008 the patient remains stable at NYHA class II with plasma CoQ₁₀ level 5.6 µg/ml and CoQ₁₀/cholesterol ratio 1.0 µmol/mmol. After 10 months of supplemental ubiquinol, his LVEDD has increased slightly from 5.4 cm to 5.7 cm.

3.6. Case #6

The patient is a 70 year old Caucasian male who suffered a large anterior wall infarct in 1993, which left him with an akinetic to dyskinetic septum and apex, and a 30% ejection fraction. The patient remained in stable NYHA class II status on standard medical therapy and ubiquinone at 120 mg/day. In early 2007 he began to deteriorate and by April 2007 reached class IV CHF with EF at 10%, with plasma CoQ₁₀ level 0.6 $\mu\text{g/ml}$ and CoQ₁₀/cholesterol ratio 0.2 $\mu\text{mol/mmol}$. Ubiquinone was increased to 450 mg/day and after one month his clinical status began to improve slightly and plasma CoQ₁₀ level was 2.0 $\mu\text{g/ml}$ and CoQ₁₀/cholesterol ratio 0.7 $\mu\text{mol/mmol}$. In June 2007 patient was changed to ubiquinol at 600 mg/day ubiquinol with plasma CoQ₁₀ level 5.7 $\mu\text{g/ml}$ and and CoQ₁₀/cholesterol ratio 1.6 $\mu\text{mol/mmol}$. By August 2007 his clinical status improved to NYHA class II with EF 20%. After eight months of ubiquinol, the patient's LVEDD decreased from 11.5 cm to 7.7 cm with a corresponding improvement in the mitral regurgitation caused by apical tethering of the mitral valve leaflets.

3.7. Case #7

The patient is a 68 year old Caucasian female who presented in 1991 with CHF, atrial fibrillation and documented normal coronary anatomy. On standard medical therapy and ubiquinone at 200 mg/day she remained stable at NYHA class II status with a 40% EF up until 2007 when she gradually deteriorated to class IV CHF and a 20% EF by May 2007. Despite increasing ubiquinone to 450 mg/day she continued to worsen and her plasma CoQ₁₀ level was 1.8 $\mu\text{g/ml}$ with CoQ₁₀/cholesterol ratio 0.6 $\mu\text{mol/mmol}$. She required frequent hospitalizations for inotropes and diuretics along with repeat thoracentesis for large pleural effusions. She was then changed to ubiquinol at 600 mg/day and within two months her clinical status improved to NYHA class II with 30% EF and plasma CoQ₁₀ increased to 7.3 $\mu\text{g/ml}$ and CoQ₁₀/cholesterol ratio 1.6 $\mu\text{mol/mmol}$. By January 2008 she remained stable NYHA class II with plasma CoQ₁₀ 8.5 $\mu\text{g/ml}$ and CoQ₁₀/cholesterol ratio 1.9 $\mu\text{mol/mmol}$. She is now recovering from severe influenza with a drop to NYHA class III CHF and 20% EF as of February 2008. After 10 months of ubiquinol, LVEDD increased from 6.5 cm to 7.5 cm with no improvement in moderate mitral regurgitation.

4. Results

We observed a dramatic increase in plasma CoQ₁₀ levels in all seven patients when switched from supplemental ubiquinone to ubiquinol with corresponding improvements in clinical status in all patients (Table 1). Echocardiographic measurements improved dramatically in four of the seven patients. Total cholesterol levels tend to be low in severe heart failure and increased as expected with improvement in congestive heart failure. No patients were on HMG-CoA reductase inhibitors (statins). Plasma vitamin E levels increased with increasing plasma CoQ₁₀ levels, presumably due to a sparing effect, with no patients taking supplemental vitamin E. We observed no increase in % oxidized CoQ₁₀ levels in severe heart failure and very little change in % oxidized CoQ₁₀ levels with higher plasma CoQ₁₀ levels after ubiquinol supplementation (Table 2). Four of the seven patients had atrial fibrillation and were on coumadin. We observed no interaction between the high plasma CoQ₁₀ levels on ubiquinol and coumadin. No side effects from ubiquinol were observed. The prognosis for patients with NYHA class IV heart failure is very poor with mortality as high as 74% at 6 months and 94% at 12 months [4]. Six of our seven patients have survived longer than we expected and remain stable between NYHA class I-III on ubiquinol now, at

Table 1
Baseline ubiquinone vs most recent ubiquinol, Individual values for each patient

Case	Plasma CoQ ₁₀ ($\mu\text{g/ml}$)	CoQ ₁₀ /Cholesterol ($\mu\text{mol/mmol}$)	EF (%)	NYHA Class	Ubiquinol (months)
#1	2.0 → 9.3	0.5 → 2.8	15 → 60	IV → I	20
#2	0.9 → 2.6	0.3 → 0.6	35 → 50	IV → III	3
#3	1.5 → 8.9	0.2 → 1.4	10 → 10	IV → III	12
#4	1.7 → 5.1	0.4 → 1.2	35 → 60	IV → I	10
#5	1.5 → 5.6	0.3 → 1.0	30 → 55	IV → II	10
#6	2.0 → 5.7	0.7 → 1.6	10 → 20	IV → II	9
#7	1.8 → 8.5	0.6 → 1.9	20 → 20	IV → III	10
Average	1.6 → 6.5	0.4 → 1.5	22 → 39	IV → II	10

EF - Ejection Fraction, NYHA - New York Heart Association

Table 2
Baseline ubiquinone vs most recent ubiquinol, Average values for all 7 patients

	Ubiquinone	Ubiquinol	Change
CoQ ₁₀ /day	450 (mg)	580 (mg)	
Plasma CoQ ₁₀	1.6 ($\mu\text{g/ml}$) (1850 nmol/l)	6.5 ($\mu\text{g/ml}$) (7052 nmol/l)	+303%
CoQ ₁₀ /Total Cholesterol	0.443 $\mu\text{mol/mmol}$	1.492 $\mu\text{mol/mmol}$	+237%
Total Cholesterol	177 (mg/dl) (4.6 mmol/l)	205 (mg/dl) (5.3 mmol/l)	+16%
Vitamin E	14 ($\mu\text{g/ml}$) (32 $\mu\text{mol/l}$)	20 ($\mu\text{g/ml}$) (45 $\mu\text{mol/l}$)	+43%
Vitamin E/Total Cholesterol	7.0 ($\mu\text{mol/mmol}$)	8.6 ($\mu\text{mol/mmol}$)	+22%
% Oxidized CoQ ₁₀	1.7%	0.7%	
% Reduced CoQ ₁₀	98.3%	99.3%	+1%

the time of writing this manuscript, for an average of 12 months (range 9 to 20 months). Unfortunately, case #2 stayed on ubiquinol for only three months and although improving in heart function, stopped all CoQ₁₀ due to cerebrovascular disease and expired three months later.

5. Discussion

All of the seven heart failure patients had considerable regions of non-viable myocardium which appears thin, echo dense and either akinetic or dyskinetic by echocardiography. These regions of non-viable myocardium, whether secondary to prior myocardial infarction or long standing dilated cardiomyopathy, cannot be expected to show improvement with supplemental CoQ₁₀. On the other hand, regions of myocardium that are viable and hypokinetic often show improved function with adequate CoQ₁₀ supplementation leading to improvement in overall heart function and clinical status. Furthermore, indices of diastolic function may show considerable improvement with CoQ₁₀ therapy, leading to improved NYHA class, even if there is little change in ejection fraction. In keeping with previous heart failure trials with CoQ₁₀, we observed no side effects or drug interactions with CoQ₁₀ therapy, including no interaction with coumadin.

All seven of these patients had right and left heart failure with pulmonary edema, ascites and leg edema. It is our assumption that intractable intestinal wall edema in these critically ill patients is impairing CoQ₁₀ absorption. We consider this a vicious cycle wherein worsening CHF leads to worsening edema with decreased CoQ₁₀ absorption, decreased CoQ₁₀ plasma CoQ₁₀ levels and further worsening of CHF

resulting in death. Up until the current experience with ubiquinol we have never been able to alter this inexorable cycle which can occur in patients previously stable for many years.

After enrolling our seven CHF patients, we decided to see if we could improve the status of a NYHA class IV heart failure patient with what was considered a therapeutic plasma CoQ₁₀ level on ubiquinone. It must be emphasized that the ideal therapeutic plasma CoQ₁₀ level remains unknown and will only become more clear when we have data on simultaneous plasma and heart muscle CoQ₁₀ levels. This additional patient was a 72 year old Caucasian female with severe ischemic cardiomyopathy, NYHA class IV symptoms and a 10% EF. Her plasma CoQ₁₀ level was very good of 6.9 $\mu\text{g/ml}$ (0.5% oxidized CoQ₁₀ and CoQ₁₀ to cholesterol ratio of 1.4 $\mu\text{mol/mmol}$) on 900 mg/day of ubiquinone. It should be noted that this patient had predominant left heart failure with only mild abdominal and leg edema which we assume is the reason for her good plasma CoQ₁₀ level. Since this patient was rapidly deteriorating and was not a candidate for heart transplant, we decided to try changing her from supplemental ubiquinone at 900 mg/day to ubiquinol at 450 mg/day. This resulted in a higher plasma CoQ₁₀ level of 11.1 $\mu\text{g/ml}$ (0.5% oxidized CoQ₁₀ and CoQ₁₀ to cholesterol ratio of 2.2 $\mu\text{mol/mmol}$). We observed no clinical or echocardiographic benefits and the patient continued to deteriorate and expired eight months later. This is just a single case and we plan on treating a few more of these desperately ill patients with ubiquinol to ascertain whether pushing plasma CoQ₁₀ levels above what is considered therapeutic has any additional benefit.

6. Summary

In 25 years of experience in treating congestive heart failure of diverse etiology with supplemental CoQ₁₀ in addition to conventional medical therapy, we have consistently seen the best response when CoQ₁₀ is begun early in the course of the disease, before permanent myocyte loss with thin and echo dense myocardium. Our experience with late stage NYHA class IV congestive heart failure has frequently been frustrated by an inability to attain plasma CoQ₁₀ levels of $>2.5 \mu\text{g/ml}$. Based upon clinical experience over the past decade, we now consider therapeutic plasma CoQ₁₀ levels to be $>3.5 \mu\text{g/ml}$.

Patients in NYHA class IV CHF often have intractable edema due to a combination of very low cardiac output, cardiac cachexia with low albumin and therefore low oncotic pressure, and the frequent occurrence of renal failure, all of which combine to make adequate diuresis very difficult. In this early experience with ubiquinol supplementation, we have observed improvement in CoQ₁₀ absorption and have attained high plasma CoQ₁₀ levels, rarely observed with any prior ubiquinone formulation. We have limited understanding of the mechanism of CoQ₁₀ intestinal absorption and it is not rare to observe poor, sub-therapeutic CoQ₁₀ levels in heart failure patients with NYHA class II or III CHF. The improvement in plasma CoQ₁₀ levels in these seven patients with an end stage congestive heart failure was associated with clinical improvement. It is likely that ubiquinol would show even more clinical benefit in early congestive heart failure and future controlled trials of Kaneka QHTM in congestive heart failure are anxiously awaited.

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