



From the Desk of Dr. Stephen Sinatra

Refractory Congestive Heart Failure Successfully Managed with High Dose Coenzyme Q₁₀ Administration

Stephen T. Sinatra, M.D., F.A.C.C., F.A.C.N., C.N.S., C.B.T

Reprinted from Molec. Aspects Med.
Vol. 18 (Supplement), pp. 299 -305



PII: S0098-2997(97)00011-3

Refractory Congestive Heart Failure Successfully Managed with High Dose Coenzyme Q₁₀ Administration

Stephen T. Sinatra

*Manchester Hospital, Manchester, CT, USA and University School of Medicine,
Farmington, CT, USA*

Abstract—Coenzyme Q₁₀ (CoQ₁₀) is a critical adjuvant therapy for patients with congestive heart failure (CHF), even when traditional medical therapy is successful. Adjunctive therapy with Q₁₀ may allow for a reduction of other pharmacological therapies, improvement in quality of life, and a decrease in the incidence of cardiac complications in congestive heart failure. However, dosing, clinical application, bioavailability and dissolution of CoQ₁₀ deserve careful scrutiny whenever employing the nutrient. The assessment of blood levels in 'therapeutic failures' appears warranted. © 1997 Elsevier Science Ltd

Keywords: bioavailability of Coenzyme Q₁₀; congestive heart failure; cardiomyopathy (idiopathic); serum assay of CoQ₁₀; HMG co-reductase inhibitors; Coenzyme Q₁₀ (ubiquinone)

Introduction

The management of congestive heart failure (CHF) is perhaps the most difficult challenge faced by most cardiologists today. In fact, as a practicing cardiologist for over 20 years, I have often found cases of refractory CHF to be among my worst nightmares. Why? Although there are excellent conventional approaches in the battle against CHF, the fact remains that many patients do not fully respond to pharmacological agents and they cannot tolerate the many side effects that often occur when employing them. Despite modern medicine and technology, quality of life is compromised and survival often remains guarded. Many, however, do improve on a combination of conventional and complementary approaches.

The following report will include two case studies of patients treated for CHF with standard conventional approaches, both of whom had been refractory to traditional

treatment alone. Even after supplementation with low dose Coenzyme Q₁₀ (CoQ₁₀) therapy, their clinical status was not markedly improved. Only after the addition of 300 mg of CoQ₁₀ therapy daily did both of these patients achieve an improvement in left ventricular function as well as a better quality of life.

Case Reports

Case 1

A 79-year-old female with a long-standing history of hypertension, was diagnosed with CHF in 1977, at age 60 years. By 1984 she had experienced her first episode of pulmonary oedema, which had been treated with a combination of ace inhibition, digoxin and diuretic therapies. Her ejection fraction at that time was reduced to 35%. Following a second episode of flash pulmonary oedema in 1992, the patient underwent cardiac catheterization which demonstrated a dilated cardiomyopathy and normal coronary arteries. She continued to be treated with standard medical care, including ace inhibition therapy and increasing doses of diuretics. Although for years her quality of life was satisfactory overall, she continued to suffer intermittent bouts of CHF. Insidiously, her condition progressively deteriorated.

By October 1994, Case 1 weighed 77 pounds and was suffering from severe end stage cardiac cachexia (New York Heart Association {NYHA} Class IV). Her ejection fraction at that time had fallen to only 10–15%, now barely enough to support her bed-to-chair existence. CoQ₁₀ therapy was initiated at 30 mg three times a day. From October to February of 1995, she continued to remain homebound. Despite the addition of Q₁₀ therapy, her quality of life had become completely unsatisfactory, with marked oedema, ascites and severe fatigue. As her respiratory status became more compromised, she required two pleural taps for bilateral pleural effusions.

In March of 1995, Case 1 was accidentally started on 300 mg of CoQ₁₀ daily. Inadvertently, her son had purchased 100 mg capsules instead of her usual 30 mg supplements, more than tripling her dose. Approximately 4 weeks later, she experienced a steady and marked improvement in her functional status.

In June of 1995, repeat echocardiogram demonstrated an improvement in her ejection fraction (20%), as well as a reduction in both mitral and tricuspid regurgitation which had been previously noted on colour flow and Doppler analyses.

By October of 1995, Case 1 was shopping and visiting relatives. In fact, she became so active that in January of 1996 she fractured her hip, necessitating major surgery for a total hip replacement! She tolerated the surgery well, despite her previously compromised cardiac status.

When last seen in September of 1996, she continued to enjoy a good quality of life and was walking with the assistance of a cane. She continues to function at an NYHA Class II status. In addition to her conventional medical therapy, she has been successfully maintained on 300 mg of CoQ₁₀ daily.

Case 2

A second case of refractory CHF on traditional therapy involves a retired ophthalmologist with a previous history of emphysema, hypertension, anteroseptal myocardial infarction (1982) and surgical repair of abdominal aortic aneurysm (1987) who presented with a history of congestive cardiomyopathy over the past few years. Case 2 had endured several hospitalizations for evaluation of repeated episodes of pulmonary oedema complicated by ventricular tachycardia.

In December of 1994, he complained of chest discomfort at rest, shortness of breath with minimal activity, and dizziness despite traditional medical interventions with Capoten, Nitropaste, Lasix and Atrovent inhaler. He was started on a multivitamin-mineral preparation and CoQ₁₀ 30 mg three times daily. He also refused angiography.

In September, 1995 he required admission for severe congestive heart failure. During an episode of flash pulmonary odema, he required intubation and IV drug support with dopamine and high dose diuretics. Although he was gradually weaned off the ventilator and continued to show slow improvement, his functional status remained at Class III–IV status. At discharge, CoQ₁₀ therapy was increased to 120 mg daily.

Subsequent Cardiolute Stress Testing demonstrated old infarction of inferior, anterior, apical and septal walls with a dilated LV and EF estimated at 20%. In October 1995, his CoQ₁₀ dose was increased to 300 mg daily in combination with his usual Captopril 50 mg tid and Lasix 80 mg bid. In December 1995, the patient's quality of life significantly improved. Lasix was reduced to 40 mg bid. An echocardiogram revealed an improved ejection fraction of 25%.

Case 2's quality of life continued to improve, resulting in a residential move to Florida to enjoy the climate. On 300 mg of CoQ₁₀ daily, he was functioning at NYHA Class II level and was walking long distances on the beach.

Discussion

As a clinical cardiologist, I have been using CoQ₁₀ since 1986 when I first prescribed 10 mg three times daily to one of my patients undergoing revascularization. Presently, I have thousands of patients in my practice taking CoQ₁₀ on a daily basis. CoQ₁₀ is on formulary at Manchester Memorial Hospital and can be administered in a variety of clinical settings including management of CHF (Table 1).

Although the medical literature is replete with multiple studies showing the efficacy of CoQ₁₀ in clinical cardiology situations, the evaluated dose–effect relationships for CoQ₁₀ have been within a narrow range. The majority of clinical studies have investigated CoQ₁₀ in doses ranging from 90 to 150 mg daily. At such doses, some patients have responded, while others have not. Consider that, for example, the most negative and yet most quoted paper on CoQ₁₀, (Permanetter *et al.*, 1992), evaluated response to a total dose of only 100 mg/day. The researchers observed no therapeutic effect in patients with dilated cardiomyopathy.

Table 1. Potential therapeutic uses of CoQ₁₀

Cardiovascular
1. Angina pectoris
2. Unstable anginal syndrome
3. Myocardial preserving agent during chemical thrombolysis
4. Myocardial preserving agent for cardiac surgery
5. Congestive heart failure
6. Toxin-induced cardiotoxicity (adriamycin)
7. Essential and renovascular hypertension
8. Ventricular arrhythmia
9. Mitral valve prolapse
10. Prevents oxidation of LDL

Permanetter's study had major flaws. First of all, blood levels were never drawn on subjects and baseline Q₁₀ levels were never documented before treatment. In addition, the subjects of Permanetter's research were Class I–III with an average ejection fraction of $39.5 \pm 11\%$ Group I and $37.6 \pm 16\%$ Group II. No Class IV patients were included. Obviously, this was a 'fairly healthy' group of patients. Another key issue to consider is 100 mg per day of CoQ₁₀, a sufficient dose to raise the blood level to a 'therapeutic window'?

In other words, is the dose adequate to affect symptoms? And, if there is symptom alleviation at this dose level, what are the profiles of the responders? How do they differ from non-responders? In one study for example, despite clinical improvement of patients, it was stated that the 100 mg dosage was too low or that other deficiencies in these patients 'slowed the therapeutic response of Coenzyme Q₁₀' (Langsjoen *et al.*, 1990). Another provocative question is whether or not Coenzyme Q₁₀ therapy at this dose level provides symptomatic relief dramatic enough in someone with a much less compromised left ventricular ejection function to be appreciated. We know, for example, that tissue levels of CoQ₁₀ in endomyocardial biopsy specimens were lower in Class IV patients as opposed to Class I and Class II subjects. These data have demonstrated a greater deficiency of CoQ₁₀ in the most severe cases of cardiomyopathy (Folkers *et al.*, 1985).

Permanetter also makes the statement that the dosage of CoQ₁₀ in their study, 33.3 mg three times daily, was the same dosage which demonstrated a tripling of the plasma concentration in another study (Lucker *et al.*, 1984). These data were similar to a preliminary study we performed evaluating the effectiveness of different preparations of CoQ₁₀ with varying bioavailability. Our results demonstrated that most preparations of CoQ₁₀ at 120 mg dosage often correlated with an increase in the blood level to only 1.5 µg/ml (Norkus, 1996). Although a blood level of 1.5 µg/ml should be approximately three times higher than the usual baseline blood level, research indicates that the therapeutic level of CoQ₁₀ is at least 2.5 µg/ml and preferably higher (Langsjoen *et al.*, 1988). Thus, a standard 100 mg dose of CoQ₁₀ is frequently insufficient in achieving a therapeutic blood level. This may have been the case in the two studies presented.

While Permanetter's study was quite thorough in the assessment of left ventricular function parameters, their results must seriously be questioned because of the study design in patient selection, dosage, and absence of blood levels. After consulting with Dr Peter Langsjoen at the International Conference in Ancona in May 1996, I have come to appreciate the importance of drawing blood levels of CoQ₁₀ whenever possible. First of all, not all CoQ₁₀ preparations are considered equal. Certainly, absorption and relative bioavailability can impact blood levels. Even if a CoQ₁₀ product has outstanding bioavailability, a lower dosage of CoQ₁₀ may still result in a sub-therapeutic serum level. With the benefit of blood levels, Dr Langsjoen and his colleagues have gained direct experience in adjusting CoQ₁₀ dosing on the basis of its achieved blood level while evaluating clinical response. This experience has provided him with extensive clinical knowledge resulting in a comfort level when treating his cardiac population at higher dose ranges. However, finding a laboratory that will draw CoQ₁₀ levels is not always a feasible option for us practitioners. It requires special laboratory equipment and highly trained personnel, not available at most hospitals.

In general, I recommend that when patients fail to respond to standard levels of CoQ₁₀ intervention, i.e. 90–150 mg, it is best to obtain a blood level. If a serum CoQ₁₀ level is not feasible, treat the patient clinically by doubling or even tripling the dose according to their clinical symptoms, as cardiologists frequently do with diuretics and/or ace inhibitors when treating congestive heart failure. We also must keep in mind that higher doses of CoQ₁₀ are required in patients with right sided symptoms, particularly since rather serious myocardial CoQ₁₀ deficiencies were found in cases with high right atrial pressures (Littarru *et al.*, 1972).

It is also important to note a subgroup of patients with CHF and co-existent coronary artery disease who are also on CoQ₁₀ depleting agents; those currently being treated with HMGCoA-reductase inhibitors to lower serum cholesterol. Cholesterol production, as well as endogenous pathways for CoQ₁₀ production, are both compromised on HMGCoA-reductase inhibition (Folkers *et al.*, 1990). This particular subpopulation of patients may need additional doses of CoQ₁₀ to offset the CoQ₁₀ depleting effects of these hypercholesterolemic agents.

Conclusion

Left ventricular function depends on the operational capacity of myocardial cells to generate the energy to expand and contract. Insufficient myocardial contractive forces often contribute significantly to CHF. Literally, heart failure is an 'energy-starved heart'. It is no longer enough for contemporary clinical cardiologists to focus on the fluid retention in pump failure. We need to consider the biochemistry of 'pulsation' as well. It is critically important for us to treat both the molecular and cellular components of the heart when managing CHF.

Therefore, as cardiologists, we must think 'bioenergetically'. CoQ₁₀ has a significant effect upon electron transfer within the respiratory chain and supports intramyocardial energy at the cellular level. Because oxygen based production of energy takes place in cellular mitochondria, it is not unusual for CoQ₁₀ concentrations in myocardial cells to be ten-fold that of the brain or the colon.

Because it is one of the few tissues of the body to function continuously in an aerobic mode, the myocardium requires a particularly elevated ATP support. Thus, any condition that causes a decrease in CoQ₁₀ could precipitate a corresponding decrease in oxidative phosphorylation of the mitochondrial respiratory chain, thus making the tissue more susceptible to free radical attack (Rauchova *et al.*, 1995).

Since the CoQ₁₀ side effect profile is minimal (less than 1%), I find it imperative to consider CoQ₁₀ as a primary nutritional adjunctive support in the treatment of congestive heart failure, dilated cardiomyopathy, and systolic–diastolic dysfunction of the left ventricle. I cannot emphasize enough the importance of dosage and bioavailability of CoQ₁₀. Although some patients may respond to an initial dose of 30 mg three times daily, many will not. For ‘therapeutic failures’, CoQ₁₀ levels should be obtained. If when such an evaluation is not possible, increasing the dosage of CoQ₁₀ according to clinical symptoms must be considered. After following the cases of these two extremely ill patients, as well as many other anecdotal cases, it has become apparent to me that the dosing of CoQ₁₀ might be managed similarly to that of other pharmacological agents such as ace inhibitors or diuretics for CHF management. For example, captopril dosing may start at 6.25 mg three times daily and increased to as much as 50 mg three times a day before a therapeutic response is appreciated. I have managed many of my CHF patients with a similar protocol, adjusting the CoQ₁₀ dose according to the clinical response.

It is encouraging that one set of researchers in Naples, Italy, projected from their findings that the treatment of every 1000 cases of CHF with CoQ₁₀ for 1 year would reduce hospitalizations by 20% (Morisco *et al.*, 1993). In our area of cost-containment, this is indeed a compelling forecast. And the reduction in human suffering and cardiac dysfunction would hasten us to look further to CoQ₁₀ as a first line defence in CHF treatment based on both clinical research trials on large cohorts and in anecdotal case studies, such as those have presented. CoQ₁₀ administration should always be performed with careful consideration to dose as well as bioavailability of the compound. Further research in this area is desperately needed.

References

- Folkers, K., Langsjoen, P. and Willis, R. (1990). Lovastatin decreases coenzyme Q₁₀ levels in humans. *Proceedings of the National Academy of Science USA*, **87**, 8931–8934.
- Folkers, K., Vadhanavikit, S. and Mortensen, S. A. (1985). Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with coenzyme Q₁₀. *Proceedings of the National Academy of Science USA*, **82**, 901–904.
- Langsjoen, P. H., Folkers, K., Lyson, K., Muratsu, K., Lyson, T. and Langsjoen, P. (1988). Effective and safe therapy with coenzyme Q₁₀ for cardiomyopathy. *Klin-Wochenschr*, **66**, 13 583–590.
- Langsjoen, P. H., Langsjoen, P. H. and Folkers, K. (1990). Long-term efficacy and safety of Coenzyme Q₁₀ therapy for idiopathic dilated cardiomyopathy. *American Journal of Cardiology*, **65**, 521–533.

- Littarru, G. P., Ho, L. and Folkers, K. (1972). Deficiency of coenzyme Q₁₀ in human heart disease. Part II. *International Journal of Vitamin Research*, **42**, 413–434.
- Lucker, P. W., Wetzelsberger, N., Hennings, G., and Rehn, D. (1984). Pharmacokinetics of coenzyme ubiquinone in healthy volunteers. *Biomedical and Clinical Aspects of Coenzyme Q*, (K. Folkers and Y. Yamamura, eds), Vol 4, pp. 143–151. Elsevier, Amsterdam.
- Morisco, C., Trimarco, C. and Condorelli, M. (1993). Effect of coenzyme Q₁₀ therapy in patients with congestive heart failure. *Clinical Investigations*, **71**, S134–S136.
- Norkus, E. P. (1996). Comparison of coenzyme Q₁₀ bioavailability from four Q₁₀-containing formulations. Unpublished Manuscript. New York Medical College.
- Permanetter, B., Rossy, W., Klein, G., Weingartner, F., Seidl, K. F. and Blomer, H. (1992). Ubiquinone (coenzyme Q₁₀) in the long-term treatment of idiopathic dilated cardiomyopathy. *European Heart Journal*, **13**, 1528–1533.
- Rauchova, H., Drahota, Z. and Lenaz, G. (1995). Function of coenzyme Q in the cell: some biochemical and physiological properties. *Physiology Research*, **44**, 209–216.