Vol. 182, No. 1, 1992 BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS
January 15, 1992 Pages 247-253

THERAPY WITH COENZYME Q_{10} OF PATIENTS IN HEART FAILURE WHO ARE ELIGIBLE OR INELIGIBLE FOR A TRANSPLANT

Karl Folkers*, Peter Langsjoen+ and Per H. Langsjoen+

*Institute for Biomedical Research, The University of Texas at Austin, Austin, Texas 78712

+1120 Medical Drive, Tyler, Texas 75701

Received September 25, 1991

Summary. Twenty years of international open and seven double blind trials established the efficacy and safety of coenzyme Q_{10} (CoQ_{10}) to treat patients in heart failure. In the U.S., ca. 20,000 patients under 65 years are eligible for transplants, but donors are less than 1/10th of those eligible, and there are many more such patients over 65, both eligible and ineligible. We treated eleven exemplary transplant candidates with CoQ_{10}; all improved; three improved from Class IV to Class I; four improved from Classes III-IV to Class II; and two improved from Class III to Class I or II. After CoQ_{10}, some patients required no conventional drugs and had no limitation in lifestyle. The marked improvement is based upon correcting myocardial deficiencies of CoQ_{10} which improve mitochondrial bioenergetics and cardiac performance. These case histories, and very substantial background proof of efficacy and safety, justify treating with CoQ_{10} patients in failure awaiting transplantation.

Biochemistry of Coenzyme(Q_{10}). Crane et al. (1) considered that therapy with CoQ_{10} is based on its functions in mitochondria, biosynthesis of ATP, and restoration of levels of CoQ_{10} in membranes. Restoration of functions include those with a high energy output as for heart muscle, and for slow, but steady energy output, involving endomembranes instead of mitochondria.

Ernster and Beyer (2) reviewed evidence on CoQ_{10} as an antioxidant in membranes, particularly in the dihydro form. These antioxidant roles involve lipid peroxidation and defense systems in cellular membranes. They considered a clinical involvement of the antioxidant role, and a use of CoQ_{10} in the treatment of myopathies, and the prevention of the ischemia-reperfusion syndrome.

Biosynthesis of CoQ_{10} in Human Tissues. There are exceptions to the dogma that all vitamins in the human body are derived only from the diet. Niacin (vitamin B_3) is derived from dietary tryptophan in the human body, and CoQ_{10} is derived from dietary phenylalanine. There are a minimum of 17

0006-291X/92 $1.50

reactions in the human body which yield CoQ_{10} from phenylalanine and acetyl CoA. Phenylalanine is converted to tyrosine, presumably by 5,6,7,8-tetrahydrobiopterin, and tyrosine is converted to p-hydroxybenzoic acid, which is the precursor of the nucleus of CoQ_{10}; Olson et al.; (3) Rudney et al. (4). Later, Friis et al. (5) elucidated the complete biosynthesis of CoQ_{10} from p-hydroxybenzoic acid. The decaprenyl side chain is derived from acetyl-CoA via mevalonic acid. Many of these reactions in the human body, which yield CoQ_{10} from phenylalanine and acetyl-CoA, indispensibly require the coenzymes of vitamin B_6, vitamin B_2 folic acid, vitamin B_{12}, niacinamid, pantothenic acid and other essential factors and trace elements.

Prediction of Human Deficiencies of CoQ_{10}. Many Americans do not have adequate levels of all the vitamins, coenzymes and trace elements for the multi-step biosynthesis of CoQ_{10} even for limited health and survival apart from optimum health and survival. A human deficiency of vitamin B_6 would reduce the conversion of tyrosine to p-hydroxybenzoic acid, and then necessarily reduce tissue levels of CoQ_{10}. The very common occurrence of the carpal tunnel syndrome in the population constitutes both biochemical and clinical evidence that a widespread deficiency of vitamin B_6 occurs; Folkers et al. (6); Ellis et al. (7).

Evidence for Human Deficiencies of CoQ_{10} in Urinary Excretion. Koniuszy et al. (8) found that 35% of 63 individuals excreted in their urine less than 10 ug of CoQ_{10}/24 hours on one or more occasions. These low levels of urinary excretion were the first indication in 1960 of human deficiencies of CoQ_{10} and possible disease state(s). Bergen et al. (9) assayed 24-hour urine collections from 72 patients with diabetes mellitus and atherosclerotic heart disease and found a great variation in the range of of CoQ_{10} excretion; The average was 71 ug/24 hours. Nine of 31 females revealed no CoQ_{10} in a 24-hour collection indicating severe deficiencies.

Evidence for Human Deficiencies of CoQ_{10} in Cardiac Biopsies from Surgery. Ca. 75% of 132 cardiac patients undergoing surgery had deficiencies in the biopsies of the activity of the succinate dehydrogenase-CoQ_{10}-reductase. They represented 13 categories of diagnosis and 12/13 of these categories showed deficiencies, ranging from 20-44% of CoQ_{10}-enzyme activity, which was impressive. The cardiomyopathies associated with diabetes showed 42% deficiencies; Folkers et al. (10); Littarru et al. (11, 12). Also, Boler et al. (13) found significant deficiencies of CoQ_{10}-enzyme activity in the cardiac biopsies from 66 patients having surgery for aortic or mitral stenosis, and cardiomyopathies associated with diabetes and other dysfunctions.

Evidence for Human Deficiencies of CoQ_{10} in the Blood of Cardiac Patients. Goto et al. (14) found that ca. 20%or 87/406 blood samples from cardiac patients showed a mean lower basal specific activity and a mean

higher percent deficiency of the succinate dehydrogenase-CoQ_{10} reductase than the corresponding values from a control group; both differences, $p < 0.001$.

Evidence for Human Deficiencies of CoQ_{10} in the Hearts of Cardiac Patients in Therapy. Mortensen et al. (15) found the levels of CoQ_{10} in biopsies from cardiac patients were higher ($p < 0.02$) than before treatment, and that the myocardial deficiency of CoQ_{10} was higher with increasing severity of disease, which was reduced by therapy. Also, the blood levels of CoQ_{10} for cardiac patients in class IV were lower ($p < 0.01$) than those in class I. Blood levels for classes III and IV were lower ($p < 0.001$) than those of classes I and II. These data correlated with effective treatment of cardiomyopathy with CoQ_{10}.

Evidence for Effective Therapy of Heart Failure with CoQ_{10} from Open Studies. Folkers et al. (16) critiqued 25 publications during 1967-1978 on treating cardiac patients in failure from 110 physicians in 41 medical institutions in Japan. This decade of clinical testing allowed the consensus that therapy with CoQ_{10} for congestive heart failure was beneficial. The six books (17) corresponding to six International Symposia, 1976- 1990, on the Biomedical and Clinical Aspects of Coenzyme Q contain ca. 57 chapters on the treatment of cardiac failure with CoQ_{10}. The consensus from these 57 chapters over 14 years is again documentation for the effectiveness and safety of CoQ_{10} to treat cardiac failure.

Examples of Definitive Open Trials on Treating Heart Failure with CoQ_{10}. Mortensen et al. (18) interpreted their long-term therapy as a "major advance" in the management of resistant myocardial failure.

DiSomma et al. (19) reported data from 65 cardiologists who treated 806 patients representing 544 with heart failure and 626 with ischemic heart disease. The clinical efficacy of CoQ_{10} was significant ($p < 0.005$) in comparison with the control group on conventional therapy.

Langsjoen et al. (29) concluded that 75-85% of 88 patients had statistically significant increases in two monitored cardiac parameters on therapy with CoQ_{10}. Langsjoen et al. (20) also recorded significantly increased survivals from treatment with CoQ_{10}.

Judy et al. (21) recorded improved long-term survival for CoQ_{10}-treated congestive heart failure patients when compared with conventionally treated patients, and also found patients in congestive heart failure to relapse when therapy with CoQ_{10} was withdrawn.

Evidence on Effectiveness of CoQ_{10} to Treat Patients in Heart Failure from Double Blind Trials. Seven international double-blind trials were conducted on therapy with CoQ_{10} of patients in heart failure. Two trials were in Japan (17); two were in the U.S. (22, 23); two were in Italy (24,

25) and one was in Germany (26). Each of these seven double-blind trials confirmed the effectiveness of CoQ_{10}.

A Dysfunction of Bioegergetics and a Deficiency of CoQ_{10} are Molecular Causes of Heart Failure. Folkers et al. (27) integrated and unified 34 years of international research on the biochemistry and on the clinical therapy with CoQ_{10} of patients in heart failure, and concluded that a dysfunction of bioenergetics and a deficiency of CoQ_{10} are molecular causes of cardiac disease, which cause the death of ca. 3,000 people daily in the U.S.

Cardiac Patients Awaiting Transplantation. Presently, there are ca. 20,000 cardiac patients under 65 years of age in the U.S. awaiting transplants, and ca. 300 patients/mo. are added to the list, and ca. 150/mo. receive transplants. It is estimated that the number of donor hearts is 1,600-2,000, yearly (28).

The Importance of Case Histories. For protection of the population, modern medicine, pharmaceutical companies, and regulatory agencies justifiably require open and double blind clinical trials on a new therapy of a disease. However essential multi-trials and statistical significance may be, actual therapeutic benefit to an individual is the most important to that individual. Case histories can be valid and educational. The following eleven cases exemplify (1) the cardiac benefit of CoQ_{10}; (2) the improved physical performance; (3) possible dimunition and termination of conventional drugs; (4) a necessary brief delay in transplantation; (5) perhaps, indefinite delay or cancellation of transplantation. The dosage of the CoQ_{10} was generally 100 mg daily, but infrequently up to 240 mg. The classifications were of the New York Heart Association.

Case Histories. M.S. was a 64-year old Caucasian female who presented her first decompensation into acute pulmonary edema from ideopathic dilated cardiomyopathy in October, 1989. Catheterization revealed normal coronary arteries, no evidence of valvular heart disease. She was managed with aggressive conventional therapy including anticoagulants, antiarrhythmic agents, digoxin, diuretics, potassium, and angiotensin converting enzyme inhibitors. By January, 1990, she had progressed only to a Class III status, with marked dyspnea and fatigue with activities of daily living. CoQ_{10} was started in January, 1990. By May, 1990, she had improved to Class II, by February, 1991, to Class I. By 5/16/91, she continued to do exceptionally well, completely asymptomatic with a very vigorous and active lifestyle; only medication was CoQ_{10}. This case represents the marked improvement in idiopathic dilated cardiomyopathy that can be obtained when CoQ_{10} is begun shortly after the first decompensation into acute pulmonary edema. The patient was begun on CoQ_{10} three months after diagnosis. She had progressed from Class III to Class IV to Class I over a period of six months. She has had complete normalization of the ejection fraction by serial echocardiography. During the first six months of therapy, she was gradually tapered off all of her conventional drugs.

I.B. was a 43-year old Caucasian male with ischemic cardiomyopathy and documented 3-vessel atherosclerotic coronary artery disease with ejection

fraction of less than 20% for whom a cardiac transplant was recommended. He was in Class III to IV, when he was begun on CoQ_{10}, April, 1991. By mid-May, 1991, his ejection fraction had improved to 40% with marked clinical improvement to Class II. By June, 1991, he had shown continued clinical improvement and there was a gradual tapering of conventional drugs.

F.B. was a 68-year old Caucasian male with advanced idiopathic dilated cardiomyopathy who had been rejected for a cardiac transplant. His cardiomyopathy was secondary to an associated severe chronic obstructive pulmonary disease. When this patient was evaluated on 3/20/86, he was in biventricular failure, despite an ejection fraction of 22% by MUGA and 41% by STI. CoQ_{10} was begun at a dose of 100 mg per day in March, 1986, and resulted in an improvement in ejection fraction by STI to 55% with full compensation in his congestive failure. The patient was able to return to the management of his business at a moderate level of activity by June, 1986. He remained quite stable and was re-examined at the transplant center in November, 1987, and was found to have significant residual myocardial impairment. His repeat pulmonary function analysis had greatly improved to the point that he was then a candidate for cardiac transplant, which he underwent successfully in November, 1987.

M.C. was a 64-year old Black male with ischemic cardiomyopathy with severely depressed ejection fraction of only 15%, Class IV, in October of 1990 with inoperable coronary disease. He was begun on CoQ_{10} in October of 1990 and by November of 1990, he had considerable improvement, both clinically and by ejection fraction which had improved from 15% to 40%. By January of 1991, he was in Class III. By February of 1991, ejection fraction had improved to 52%, and by April of 1991, he was Class I with no limitation whatsoever on his activities or lifestyle.

J.H. was a 62-year old Caucasion male with severe ishemic cardiomyopathy, Class IV, with an ejection fraction of 15%, and 3-vessel atherosclerotic coronary artery disease, judged to be inoperable. He was begun on CoQ_{10} in February of 1988 and by August of 1989, had a decrease in left ventricular end-diastotic dimension from 7.7 cm to 5.3 cm by echo. By March of 1990, he had a completely normal left ventricular size with normal ejection fraction by echo. The patient continued to do well in the spring of 1991, as in functional Class II, related to severe chronic obstructive pulmonary disease.

P.B. was a 43-year old Caucasian male with idiopathic dilated cardiomyopathy with acute decompensation with pulmonary adema and marked enlargement of the heart with normal coronary arteries in July, 1987. He was begun on CoQ_{10}. He showed gradual improvement in clinical status as well as echocardiographic improvement in heart size and function over the following two years. Then, he was in Class I with completely normal ejection fraction and normal heart size. As of July, 1991, he continues an extremely active athletic lifestyle with his only medication being CoQ_{10}.

J.T. was a 46-year old Caucasian male with ischenic cardiomyopathy, Class III to IV. He was begun on CoQ_{10} in March, 1987, with an excellent clinical response. By June of 1991, he had a Class II status with improvement in left ventricular size from 7.4 cm to 5.9 cm. His well-preserved ejection fraction markedly improved from his baseline.

C.B. was a 66-year old Caucasian male with idiopathic dilated cardiomyopathy in April, 1988, and with enlarged and poorly functioning left ventricle and normal coronary arteries. With conventional management, he was, at best, in Class III. CoQ_{10} was begun in May, 1989. By January, 1991, he was in Class II. By June of 1991, he was in Class I with a completely normal echocardiogram. CoQ_{10} was his only medication.

F.F. was a 50-year old Caucasian male with idiopathic dilated cardiomyopathy, Class IV, with MUGA ejection fraction of only 14%. He was started on CoQ_{10} in April, 1991. By the end of May, 1991, his ejection fraction had improved from 14% to 40%, and the patient was in Class I with no limitations of activity.

L.F. was a 55-year old Caucasian female with idiopathic dilated cardiomyopathy, Class III to IV, August, 1987. Her ejection fraction was 25 to 30%. She was begun on CoQ_{10} in August, 1987. By October, she was was Class II to III. By December, 1987, the left ventricular end-diastolic dimension had decreased from 6.8 cm to 4.6 cm. By January, 1991, the ejection fraction was well within normal limits at 60% She continued to do exceptionally well in Class II; symptoms were largely attributed to severe obstructive airways disease.

L.G. was a 55-year old Caucasian male with severe ischemic cardiomyopathy, Class III, with MUGA ejection fraction of 16%. He was begun on CoQ_{10} in January, 1991., with marked clinical improvement by one month. By March, 1991, his ejection fraction had improved to 50%, and he was in Class II.

Acknowledgment. Appreciation is expressed to the Robert A. Welch Foundation of Houston, Texas for financial support during a 23-year period.

REFERENCES

1. Crane, F.L., Sun, I.L., Sun, E. and Morre, D.J., (1991) Biomedical and Clinical Aspects of Coenzyme Q, K. Folkers and Y. Yamamura, Eds., Elsevier, New York, Vol.6, 59-70.
2. Ernster, L. and Beyer, R.E. (1991) Biomedical and Clinical Aspects of Coenzyme Q, K. Folkers and Y. Yamamura, Eds., Elsevier, New York, Vol. 6, 45-58.
3. Olson, R.E., Bentley, R., Aiyar, A.S., Dialameh, G.H., Gold, P.H., Ramsey, V.G. and Springer, C.M. (1963) J. Biol. Chem., 238, 3146-3148.
4. Parson, W.W. and Rudney, H. (1964) Proc. Natl. Acad. Sci. USA, 51, 444-450.
5. Friis, P., Daves, D, Jr., and Folkers, K. (1966) J. Am. Chem. Soc., 88, 4754-4756.
6. Folkers, K., Ellis, J.M., Watanabe, T., Saji, S. and M. Kaji (1978) Proc. Natl. Acad. Sci. USA, 75 (7), 3410-3412.
7. Ellis, J.M., Folkers, K., Levy, M., Shizukuishi, S., Lewandowski, J., Nishii, S., Schubert, H.A. and R.F. Ulrich (1982) Proc. Natl. Acad. Sci. USA, 79, 7494-7498.
8. Koniuszy, F.R., Gale, P.H., Page, A.C., Jr. and Folkers, K. (1960) Arch. Biochem. Biophys., 87, No. 2, 298-305.
9. Bergen, S.S., Koniuszy, F.R., Page, A.C., and Folkers, K. (1961) Arch. Biochem. Biophys., 95, 348-351.
10. Folkers, K., Littarru, G.P., Ho, L., Runge, T.M., Havanonda, S., and Cooley, D. (1970) Int. J. Vit. Nutr. Res., 40, 380-390.
11. Littarru, G.P., Ho, L., and Folkers, K. (1972) Int. Vit. Nutr. Res., 40, 291-305.
12. Littarru, G.P., Ho, L., and Folkers, K. (1972) Int. Vit. Nutr. Res., 42, 413-434.
13. Boler, J.B., Farley, T.M., Scholier, J. and Folkers K. (1969) Intern. J. Vitamin Res., 39, 3, 281.
14. Goto, Y., Wada, Y., Katushima, I. (1969) Rinsho to Kenkyu., 46, 1192-1197.
15. Mortensen, S.A., Vadhanavikit, S., and Folkers, K. (1984) Drugs Exptl. Clin. Res., 10 (7), 497-502.

16. Folkers, K., Watanabe, T., and Kaji, M. (1977) J. Molecular Med., 2, 431-460.
17. Biomedical and Clincal Aspects of Coenzyme Q, K. Folkers and Y. Yamamura, Eds., New York, Vol. 1, 1977; Vol. 2, 1979; Vol. 3, 1981; Vol. 4, 1983; Vol. 5, 1985; Vol. 6, 1991.
18. Mortensen, S.A., Vadhanavikit, S., Baandrup, U. and Folkers, K. (1985) Drugs Exptl. Clin. Res. XI (8), 581-593.
19. Langsjoen, P.H., Folkers, K., Lyson, K., and Muratsu, K. (1988) Klinische Wochenschrift, 66, 583-590.
20. Langsjoen, P.H., Folkers, K., Lyson, K., Muratsu, K., Lyson, T., and Lansjoen, P., unpublished data.
21. Judy, W.V., Folkers, K., and Hall, J.H. (1991) Biomedical and Clinical Aspects of Coenzyme Q, Vol. 6, Elsevier, New York, 283-298.
22. Mortensen, S.A., Vadhanavikit, S., and Folkers K. (1985) Proc. Natl. Acad. Sci. USA, 82, 4240-4244.
23. Judy, W.V., Hall, J.H., Toth, P.D., and Folkers, K. (1985) Biomedical and Clinical Aspects of Coenzyme Q, K. Folkers and Y. Yamamura, Eds., Vol. 5, Elsevier, New York, 315-323.
24. Rossi, E., Lombardo, A., Lippa, S., Oradei, A., Littarru, G.P., and Manzoli, U. (1991) Biomedical and Clinical Aspects of Coenzyme Q, Vol. 6, K. Folkers and Y. Yamamura, Eds., Elsevier, New York, 321-326.
25. Ursini. T., Gambini, C., Paciaroni, E., Littarru, G.P. (1991) Biomedical and Clinical Aspects of Coenzyme Q, Vol. 6, K. Folkers and Y. Yamamura, Eds., Elsevier, New York, 479-480.
26. Schneeburger, W., Muller-Steinwachs, J., Anda, L.P., Fuchs, W., Zilliken, F., Lyson, K., Muratsu, K., and Folkers, K. (1985) Biomedical and Clinical Aspects of Coenzyme Q, Vol. 5, K. Folkers and Y. Yamamura, Eds., Elsevier, New York, 325-333.
27. Folkers, K., Langsjoen, P., Langsjoen, P.H., and Mortensen, S.A. (In Press) Proc. Natl. Acad. Sci. USA.
28. Private Communication, Lynne W. Stevenson, M.D., Director, Ahmanson-UCLA Cardiomyopathy Center, Division of Cardiology, UCLA School of Medicine, 47-123 CHS, 10833 Le Conte Avenue, Los Angeles, CA 90024-1679.
29. DiSomma, S., and Carati, L. (1991) Biomedical and Clinical Aspects Coenzyme Q, Vol. 6, K. Folkers and Y. Yamamura, Eds., Elsevier, New York, 257-265.