Response of Macrocytic Anemia in Children to the Coenzyme Q_4-Chromanol

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A VITAMIN E-responsive macrocytic anemia in children has been described.[1] The general nature of the anemia and its response to tocopherol are similar to that of the anemia which accompanies vitamin E deficiency in the monkey.[2,3] The monkey with anemia and creatinuria of vitamin E deficiency responds to treatment with the 6-chromanol of hexahydrocoenzyme Q_4.[4] The present report describes the response of children with macrocytic anemia to treatment with the Q_4-chromanol. This is the first report of a clinical response to a member of the coenzyme Q group.

EXPERIMENTAL

Four children with macrocytic anemia were selected for study. The general nature of the anemia, the dietary background of the children and their response to therapy with vitamin E have been described.[1] All the experimental procedures except treatment were identical to those employed in the study with vitamin E therapy.[1] The children ranged in age from seven to nineteen months. After the preliminary observation period they were given 300 mg. of the 6-chromanol of hexahydrocoenzyme Q_4 orally every day for seven days. The same observations were made as in the preceding study.[1]

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Supported in part by U. S. Public Health Service Grant No. A-5499, NTN and ONR Contract No. NONR 2149 (04). (Coenzyme Q XLV in the Coenzyme Q Series from the Merck Sharp & Dohme Research Laboratories.)

RESULTS

Peripheral Blood and Urinary Creatine-Creatinine Ratios

The response of an anemic child (Case IV) to the Q_4-chromanol is shown in Figure 1. An increase in numbers of reticulocytes was observed followed by an increase in the number of peripheral erythrocytes. The more rapid increase in erythrocytes than in hemoglobin or hematocrit was observed in all cases. The bone marrow is described in more detail later. It is of interest that this patient exhibited a serum tocopherol level within the normal range. Urinary creatine-creatinine ratios were slightly reduced during therapy but promptly increased following discontinuation of chromanol administration.

Figure 2 presents data in Case III illustrating the least effective response to the chromanol. There was no sharp reticulocyte peak as observed in Case IV. The bone marrow response was less convincing as was the response in creatine excretion. This patient exhibited a low serum tocopherol concentration, and when she was treated subsequently with vitamin E a further reticulocyte response was obtained and the bone marrow reverted to normal.

A comparison of the hematologic response to vitamin E and Q_4-chromanol treatment is given in Table I. In three cases the reticulocyte response to the chromanol was not as great as anticipated, based on prior cases of vitamin E treatment; in one case a greater response was obtained with chromanol. The erythrocyte increase following chromanol ad-

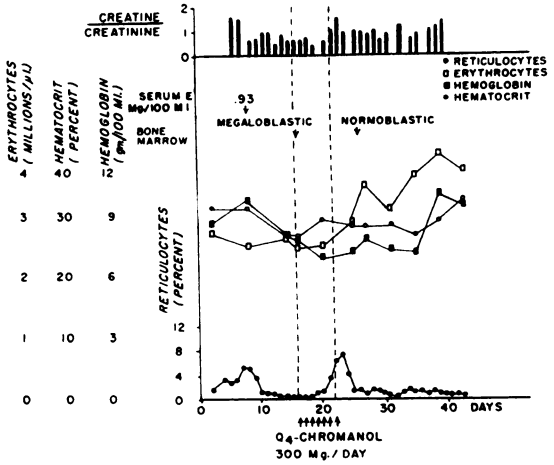

FIG. 1. Response of a nineteen month old anemic girl (Case IV) to treatment with Q_4-chromanol.

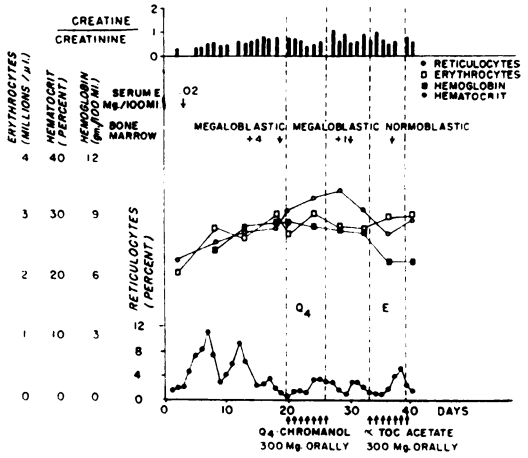

FIG. 2. Response of a seven month old anemic boy (Case III) to treatment with Q_4-chromanol and with vitamin E.

ministration was as great as the predicted response to vitamin E therapy.

Figure 3 illustrates the response of the macrocytosis to treatment with Q_4-chromanol; the mean corpuscular volume was rapidly reduced following the treatment. The reduction in mean cell volume following chromanol treatment was considerably greater than that observed in children treated with vitamin E. The interpretation of this observation must await studies of iron kinetics. The peripheral smears of all these patients made before treatment showed macrocytoses, striking anisocytosis and poikilocytosis.

Creatine-creatinine ratios before and after treatment are summarized in Table II. In three of the cases creatine excretion was reduced following treatment with Q_4-chromanol. The reduction was greatest in those patients with the highest creatine-creatinine ratios before treatment.

Bone Marrow Responses to Q_4-Chromanol

The general picture of marrow before treat-

TABLE I
Hematologic Response to Q_4-Chromanol

Case No.	Initial Erythrocyte Count (millions/μl.)	Reticulocyte Response (%)		Erythrocyte Increase (millions/μl./wk.)	
		Observed	Expected*	Observed	Expected*
I	2.60	15.0	7.5	0.30	0.24
II	2.45	6.5	9.5	0.37	0.31
III†	2.70	3.5	6.0	...	...
IV	2.42	7.5	10.5	0.55	0.32

* Expected response to vitamin E as calculated from Figure 2.[1]

† This patient was given vitamin E after the chromanol; therefore, the erythrocyte increase due to Q_4-chromanol treatment could not be calculated.

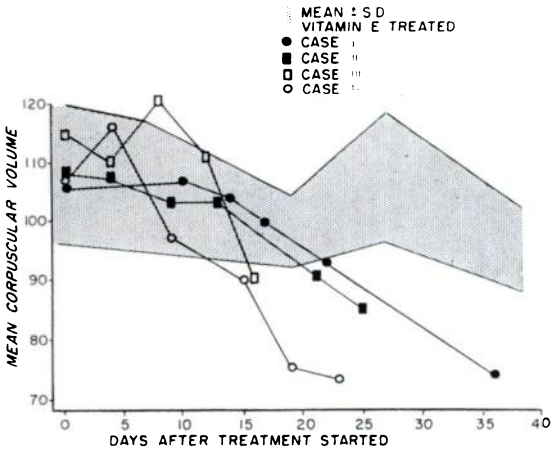

FIG. 3. Response of macrocytosis to treatment with Q_4-chromanol. The vitamin E response is the mean ± 1 standard deviation of seven cases from previously studied children.[1]

TABLE II
Urinary Creatine-Creatinine Ratios of Anemic Children Before and After Treatment with the Chromanol of Hexahydrocoenzyme Q_4

Case No.	Urinary Creatine-Creatinine Ratio	
	Before Treatment*	After Treatment†
I	1.24	0.83
II	1.03	0.67
III	0.63	0.54
IV	0.73	0.72

* Averages of the five days preceding treatment.
† Averages of the last five days of chromanol administration.

ment in all four cases was similar. It was characterized by hyperactivity, an increase in immature erythroid elements and the appearance of multinucleated erythrocyte precursors and megaloblasts. The red cell precursors seen were seldom beyond the stage of basophilic megaloblasts in their development. Abnormal mitosis was seen. The first post-treatment observations were made eight to twelve days after treatment was started. In all cases, treatment with the Q_4-chromanol resulted in definite marrow changes. The marrow became predominantly normoblastic, and the multinucleated erythroid cells disappeared, with a definite increase in the more mature forms. However, in none of the cases was the response to Q_4-chromanol complete. Megaloblasts and white cell changes persisted after treatment, and the general picture was reminiscent of partially treated pernicious anemia.

Levels of Coenzyme Q_{10} in Blood

A highly specific organic reaction between coenzyme Q_{10} and ethyl cyanoacetate has been used to devise a method for the determination of human urinary levels of coenzyme Q_{10}.[5] This method has been revised for application to human blood; it has been found that the normal human blood levels of coenzyme Q_{10} have been in the general range of 0.6 to 1.2 μg. per ml.[6]

Table III contains data on the blood levels of coenzyme Q_{10} in typical children with macrocytic anemia some of whom have been treated with either alpha tocopherol or the 6-chromanol of hexahydrocoenzyme Q_4. It is evident that these children possess coenzyme Q_{10} in the blood. Blood from normal children who otherwise correspond to these anemic children is not yet available for comparison, but the available information indicates that these children were not deficient in coenzyme Q_{10}.

COMMENTS

By all criteria available, urinary creatine excretion, hematologic response and marrow changes, these anemic children responded favorably to treatment with the Q_4-chromanol. It is of interest that the poorest response to Q_4-chromanol occurred in the patient with the lowest serum tocopherol level (0.02 mg. per 100 ml.). This may suggest that the Q_4-chromanol is effective only in the presence of vitamin E. The fact that a definite hematologic response to the Q_4-chromanol occurred in a child with normal serum tocopherol levels (Case IV) may indicate that both the Q_4-chromanol

TABLE III
Blood Levels of Coenzyme Q_{10}

Case No.	Age (mo.)	Sex	Weight (kg.)	Treatment	Coenzyme Q_{10} Level (μg. per ml. blood)
58365	18	M	9.6	Vitamin E	1.3
59188	20	F	...	None	1.5
59237	19	M	8.6	Q_4-chromanol	1.5
58858	18	M	7.4	Vitamin E	1.4

or some closely related metabolite and vitamin E are required for erythropoiesis.

From the data available it is not possible to determine the relative effectiveness of the Q_4-chromanol and vitamin E in treatment of the anemia. The two forms of treatment are not strictly comparable. Although the total dosage of each agent was approximately the same, a portion of the vitamin E was administered parenterally (250 mg. alpha tocopherol acetate orally and 100 mg. alpha tocopherol phosphate intramuscularly per day for five days). The possibility of absorption defects in these children has been pointed out,[1] and parenterally administered Q_4-chromanol might have been more effective.

It is now evident that both alpha tocopherol (which is also a 6-chromanol derivative) and the 6-chromanol of hexahydrocoenzyme Q_4 show the same hematologic and creatine response, at least qualitatively, in such anemic children. This finding is comparable to that previously reported[4] on the response of the anemic and dystrophic monkeys to treatment with both alpha tocopherol and the Q-chromanol. For these biologic responses in the Rhesus monkey and the anemic children, one may consider the following questions: (1) Are both vitamin E and the Q-chromanol exhibiting an intrinsic biologic activity? (2) Is only vitamin E or the Q-chromanol exhibiting an intrinsic activity with the other substituting solely on the basis of similarity of chemical structure? (3) Is either the vitamin E or Q-chromanol merely protecting the other because of nonspecific antioxidant properties? Although the natural occurrence of vitamin E as chromanols is well recognized, the participation of chromanol forms of coenzyme Q in biochemical transformations is not established on the basis of isolation and characterization. However, chromanols of the coenzyme Q group have shown biologic activity *in vivo*.

SUMMARY

Four children with macrocytic anemia have been treated with the 6-chromanol of hexahydrocoenzyme Q_4. Urinary creatine-creatinine ratios were reduced following treatment in three of these patients. Following Q_4-chromanol treatment, reticulocytes increased with improvement in the anemia, and the bone marrow changed from predominantly megaloblastic to predominantly normoblastic. Q_4-chromanol treatment resulted in dramatic reduction in the previously elevated mean corpuscular volumes.

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