Effect of abnormal liver function on vitamin E status and supplementation in adults with cystic fibrosis

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SUMMARY Patients with cystic fibrosis tend to have reduced serum concentrations of vitamin E and are therefore at risk of developing the neurological complications associated with vitamin E deficiency. Improved survival in cystic fibrosis has resulted in an increasing number of older patients who may develop hepatobiliary complications which may further impair the absorption of vitamin E. In this study the vitamin E status and results of supplementation with oral vitamin E were compared in adult patients with and without evidence of liver involvement as assessed by routine liver function tests. The serum vitamin E concentrations were reduced below normal in 24 of 25 patients. The mean serum vitamin E concentration was significantly lower ($p < 0.05$) in those patients with abnormal liver function. When vitamin E status was assessed as the serum vitamin E/cholesterol ratio, however, there was no significant difference between those patients with normal and abnormal liver function. After supplementation with oral vitamin E, either 10 mg/kg/day for one month or 200 mg/day (equivalent to 3.4 to 4.4 mg/kg/day) for up to three months, there was no significant difference in the vitamin E status between the two groups. The results of this study indicate that in general, patients with cystic fibrosis and abnormal liver function do not require increased supplements of vitamin E compared with those with normal liver function.

A severe deficiency of vitamin E resulting from prolonged fat malabsorption is a recognised cause of a spinocerebellar disorder comprising areflexia, ataxia, and proprioceptive loss. This syndrome has been described in abetalipoproteinaemia¹⁻³ and in children with chronic liver disease.⁴⁻⁸ It has also been reported in a few cases of adults and children with extensive ileal resection⁹⁻¹⁰ and patients with cystic fibrosis.¹¹⁻¹³

Reduced serum concentrations of vitamin E have been frequently documented in children and adults with cystic fibrosis¹⁴⁻¹⁷ but the development of overt neurological disease is, relatively rare. In the patients in whom it has been described there have been complications in addition to pancreatic insufficiency which would be expected to further impair absorption of fat and the fat soluble vitamins such as vitamin E. Thus the two patients reported by Elias *et*

*al*¹¹ had a luminal bile salt concentration which was below the critical micellar concentration and hepatomegaly respectively. The other cases in whom clinical details are available had multiple ileal resections¹² or severe liver disease.¹³ In a study of 29 unselected patients who had no neurological symptoms one patient had definite reflex and sensory abnormalities and another two were abnormal on neurophysiological grounds.¹³ Neurological abnormalities were found in 1.5 and 2.5% patients in two other series of patients with cystic fibrosis.^{18 19}

Adequate luminal bile salt concentrations are necessary for the efficient solubilisation and absorption of such hydrophobic compounds as tocopheryl acetate (vitamin E acetate).^{20 21} Patients with cystic fibrosis have an increased faecal loss of bile salts²² which can result in a reduced bile salt pool and reduced intraluminal bile salt concentrations.²³ The prevalence of hepatobiliary disease in cystic fibrosis has increased with improved survival²⁴ and in patients with this complication there may be a further reduction in intestinal bile salt concentrations.

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Received for publication 9 September 1985

The purpose of this study was therefore to document the effect of abnormal liver function on the vitamin E status and ease of supplementation of adults with cystic fibrosis. This would provide information as to whether patients with abnormal liver function tended to have lower serum concentrations of vitamin E and whether they might require higher doses of vitamin E supplements to maintain normal serum concentrations.

Methods

PATIENTS

Twenty five adult patients with cystic fibrosis (15 men, 10 women) from the Brompton Hospital, London, were studied. All had a sweat sodium concentration greater than 70 mmol/l and had the typical clinical features of the condition including pancreatic insufficiency. Their mean age was 24.6 years (range 17–41 years).

Liver function was assessed by measurement of serum alkaline phosphatase, aspartate aminotransferase and gamma glutamyl transpeptidase activities. The activities of all these enzymes were consistently normal (measured on at least two occasions) in 16 patients (eight men, eight women) and they were classified as having normal liver function. The other nine patients (seven men, two women) had abnormal liver function tests as defined by activities of alkaline phosphatase which were consistently greater than 250 IU/l (normal range 50–200 IU/l) and a consistent rise of aspartate aminotransferase (normal range 5–17 IU/l) and/or gamma glutamyl transpeptidase (normal range 5–28 and 3–14 IU/l for men and women respectively). The spleen was palpable, suggesting a degree of portal hypertension, in six of the nine patients with abnormal liver function which suggests a degree of portal hypertension, although none of them had evidence of oesophageal varices. In none of the patients with normal liver function was the spleen palpable. Patients who had only raised alkaline phosphatase or a transient rise in the other enzymes were not included in the study. All the patients were receiving pancreatic enzymes and a multivitamin supplement (which did not contain vitamin E) before and during the course of the study.

In all of the patients, serum vitamin E estimations were carried out before and after supplementation with oral vitamin E (10 mg/kg body weight/day) for one month. In some of them a lower dose of vitamin E (200 mg/day, equivalent to 3.4 to 4.4 mg/kg/day) was then evaluated.

Serum vitamin E concentrations were measured colorimetrically²⁵ and cholesterol concentrations were estimated enzymatically using a commercial kit

supplied by Abbott Laboratories Limited. All the specimens were coded. The code was broken at the end of the first supplementation study. Liver function tests were undertaken by routine methods. Results are expressed, unless stated otherwise, as mean $\pm$ 1SD and the significance of differences between mean values was calculated by the two tailed Student's *t* test.

Results

VITAMIN E STATUS BEFORE SUPPLEMENTATION

The mean age of the patients with normal liver function was greater ($p < 0.01$) than those with abnormal liver function (28.0 ± 6.3 and 21.2 ± 1.9 years respectively). The serum cholesterol concentrations and vitamin E status are shown in Figure 1. Only one patient (with normal liver function) had a normal serum vitamin E concentration (normal range 11.5 to 35.0 $\mu\text{mol/l}$ ²⁵), whereas when vitamin E status was expressed as the serum vitamin E/cholesterol ratio, three patients (all with normal liver function) had normal ratios (greater than 2.1 $\mu\text{mol}/\text{mmol}$). The serum cholesterol concentrations in the two groups were similar; 3.6 ± 0.9 and 3.2 ± 0.8 mmol/l for those with normal and abnormal liver function respectively (normal range being 2.9 to 7.8 mmol/l²⁶). The patients with abnormal liver function had a mean serum vitamin E concentration which was just significantly lower ($p < 0.05$) than that of patients with normal liver function (3.0 ± 1.6 and 6.2 ± 4.3 $\mu\text{mol/l}$ respectively). There was, however, no significant difference in the serum vitamin

Fig. 1 Serum cholesterol concentrations and vitamin E status of adults with cystic fibrosis. ● patients with normal liver function, ○ patients with abnormal liver function, — — — denotes the lower limit of normal.

E/cholesterol ratios (1.1 ± 0.6 and 1.7 ± 0.9 $\mu\text{mol}/\text{mmol}$ for those with abnormal and normal liver function respectively).

VITAMIN E CONCENTRATIONS AFTER SUPPLEMENTATION

Tocopheryl acetate 10 mg/kg/day

Fifteen patients (eight with normal and seven with abnormal liver function) were given vitamin E in the form of DL alpha tocopheryl acetate (Ephynal-Hoffmann La Roche & Co) at a dose of 10 mg/kg/day for one month. The increase in serum vitamin E concentrations and vitamin E/cholesterol ratios over time are shown in Figure 2. There were no significant differences between the two groups in the mean rise of the serum vitamin E concentrations (15.2 ± 7.2 and 12.6 ± 7.3 $\mu\text{mol}/\text{l}$) or in the mean rise in the vitamin E/cholesterol ratios (4.5 ± 1.9 and 4.5 ± 2.5 $\mu\text{mol}/\text{mmol}$) in the patients with normal and abnormal liver function respectively).

In all except three patients (one with normal and two with abnormal liver function) the serum vitamin E concentrations reached the normal range within one month. These three patients were treated for longer with 10 mg/kg/day of vitamin E and they all had normal serum concentrations of vitamin E after a further four to six months of supplementation (9.7 increasing to 18.1, 3.5 to 12.2, and 9.1 to 13.4 $\mu\text{mol}/\text{l}$). Only one of these patients (who had abnormal liver function), had a vitamin E/cholesterol ratio below normal (0.8 $\mu\text{mol}/\text{mmol}$) and this rose to within the normal range (2.8 $\mu\text{mol}/\text{mmol}$) after a further six months of treatment.

Tocopheryl acetate 200 mg/day

After the trial of 10 mg/kg/day of vitamin E, eight of

Fig. 2 Vitamin E status after supplementation with tocopheryl acetate (10 mg/kg/day) ●—● patients with normal liver function, ○—○ patients with abnormal liver function, — — — denotes the lower limit of normal.

the patients were requested to continue on this dose but compliance was erratic. After an interval of one to seven months serum vitamin E concentrations were again measured and the patients were then instructed to take just one tablet of tocopheryl acetate daily (200 mg/day equivalent to 3.4–4.4 mg/kg/day) and concentrations of the vitamin were measured after a further one to three months. Details of the vitamin E intake between the two trials and the serum vitamin E concentrations before and after the reduced dose of 200 mg/day are shown in the Table. In patients 1 and 5 serum vitamin E

Table Details and vitamin E status of patients given 200 mg/day tocopheryl acetate

Patient	Liver function	Vitamin E – 10 mg/kg/day		Period between 2 supplements		Vitamin E – 200 mg/day		
		Vitamin E conc (μmol/l)	after 1 month	Time (mn)	Claimed vit E intake mg/kg/day	Vitamin E conc (μmol/l)		Time on supplement (mn)
		Start				Start	End	
1	Normal	4.5*	27.1	6	10	39.6	28.8	3
2	Normal	9.4	23.3	2	9†	10.6	18.9	1
3	Normal	3.3	16.2	5	9	11.4	15.3	1
4	Normal	4.6	16.4	4	8	17.5	15.1	2
5	Abnormal	5.3	29.4	1	10	38.4	25.7	2
6	Abnormal	3.1	20.5	7	4‡	9.2	12.2	1
7	Abnormal	5.6	16.4	5	7	12.2	12.9	1
8	Abnormal	1.4	3.5	3	10	12.2	6.1	3

*Normal range 11.5 to 35.0 $\mu\text{mol}/\text{l}$.

†Did not take any vitamin E for one week immediately before start of second supplement (200 mg/day).

‡Took an increased dose (approx. 11 mg/kg/day) immediately before start of second supplement (200 mg/day).

concentrations decreased from supranormal to normal. They had maintained their large dose of vitamin E (10 mg/kg/day) between the two study periods. In the other patients, with the exception of patient 8, serum vitamin E concentrations tended to rise from a starting level which was around the lower limit of normal. Patient 8 whose serum concentration of vitamin E fell from 12.2 to 6.1 $\mu\text{mol/l}$ after three months on the lower dose of the vitamin had the highest activities of alkaline phosphatase and aspartate transaminase recorded in this study (2900 and 83 IU/l respectively). With this one exception there was no difference in response between those patients with normal and abnormal liver function.

Discussion

The purpose of this study was to determine whether adult patients with cystic fibrosis and evidence of abnormal liver function differed in their vitamin E status and response to supplements of the vitamin compared with similar patients with normal liver function. There has recently been discussion in the literature as to the best way of defining vitamin E deficiency. It has been suggested that serum vitamin E concentrations should be expressed per total lipid or cholesterol concentrations.²⁷⁻²⁹ In conditions such as cholestatic liver disease serum lipid concentrations tend to be increased and thus a patient with an apparently normal serum vitamin E concentration may have a reduced vitamin E/lipid ratio and possible vitamin E deficiency.²⁹ In our patients, however, serum cholesterol concentrations tended to be reduced and therefore the opposite – that is, a normal ratio with a reduced serum vitamin E concentration, might be expected.

In this study vitamin E status was assessed by serum vitamin E concentrations and the serum vitamin E/cholesterol ratio. Using both these indices the majority of patients had vitamin E deficiency. This is in agreement with a number of previous studies in both children and adults¹⁴⁻¹⁷ with cystic fibrosis. Of the 25 patients studied, only one had a normal serum vitamin E concentration whereas in three the vitamin E/cholesterol ratio was normal.

When the patients were divided according to their liver function tests, the mean serum vitamin E concentration in the patients with abnormal liver function was just significantly lower ($p < 0.05$) than that of patients with normal liver function. A corresponding difference was not, however, apparent when the mean vitamin E/cholesterol ratios were compared.

In an earlier study in children with cystic fibrosis¹⁶ we reported that normal serum concentrations of

vitamin E could be achieved within one month on a dose of 10 mg/kg/day of the fat soluble preparation of the vitamin. The same dose was therefore, used for a similar period in this study. The majority of the patients (12 out of 15) achieved normal serum concentrations after one month and only one failed to achieve a normal vitamin E/cholesterol ratio. There were no significant differences after supplementation in the mean serum concentrations and ratios between the patients with normal and abnormal liver function. After this dose of 10 mg/kg/day and a period of variable vitamin E intake we observed that a normal vitamin E status could be maintained in all except one patient with a dose of 200 mg/day (equivalent to 3.4–4.4 mg/kg/day). The exception was the patient with the highest activities of alkaline phosphatase and aspartate aminotransferase.

Because of the relationship between severe vitamin E deficiency and neurological dysfunction¹ and in view of the uncertainty about the degree of vitamin E deficiency required to cause neurological dysfunction, it seems prudent to suggest that where possible serum vitamin E status should be measured in all patients with cystic fibrosis and maintained within normal limits by appropriate supplementation. If it is not possible to regularly monitor serum vitamin E concentrations we would suggest an initial dose of 10 mg/kg/day for at least one month followed by a maintenance dose of 200 mg/day – for example one tablet of Ephynal. This dosage schedule appears to be adequate for all adult patients with the exception of those with grossly abnormal liver function tests. In these latter patients, we would strongly advise that serum vitamin E concentrations are regularly estimated and that the dosage of vitamin E is adjusted accordingly.

Such a policy of supplementing deficient patients would be more practical than carrying out regular detailed neurological assessments and starting treatment only when neurological dysfunction becomes clinically evident. It would have the important advantage of preventing neurological disability which may become more prevalent as the population of patients with cystic fibrosis grows older as a result of improved medical management.

RJS was supported by the Frances and Augustus Newman Foundation and DPRM thanks Hoffmann La Roche and Co for their continuing support.

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