Absorption of Different Doses of Fat Soluble and Water Miscible Preparations of Vitamin E in Children with Cystic Fibrosis

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Harries, J. T., and Muller, D. P. R. (1971). *Archives of Disease in Childhood*, 46, 341. **Absorption of different doses of fat soluble and water miscible preparations of vitamin E in children with cystic fibrosis.** A comparison of the intestinal absorption of water miscible and fat soluble preparations of α -tocopheryl acetate in children with cystic fibrosis showed the water miscible preparation to be more efficiently absorbed. In the absence of liver disease, a daily dose of 1 mg/kg body weight of a water miscible preparation can be expected to correct any pre-existing vitamin E deficiency within 2 months of starting treatment, and is adequate for subsequent maintenance.

Vitamin E deficiency due to intestinal malabsorption is frequently found in children with cystic fibrosis (CF) (Bennett and Medwadowski, 1967; Muller and Harries, 1969). The mechanisms that influence the absorption of vitamin E in the normal child are not yet fully understood and the precise cause of its malabsorption in CF is not clear. Bile salt micelles play an important role in the solubilization and absorption of dietary lipids from the intestinal lumen (Hofmann and Borgstrom, 1962), and it is probable that incorporation of monoglycerides and fatty acids into the bile salt micelle is of major importance for the solubilization of fat soluble vitamins (Badley, 1970). Since monoglycerides and fatty acids are liberated from dietary triglyceride by the action of pancreatic lipase, the defective lipolysis in patients with CF might be anticipated to interfere with the absorption of fat soluble vitamins such as vitamin E. Water miscible preparations of vitamin E, therefore, by being less dependent on this solubilizing system, are likely to be more efficiently absorbed than fat soluble preparations.

In a preliminary communication we reported that a water miscible preparation of α -tocopheryl acetate was better absorbed than a fat soluble

preparation in children with CF when given in a large dose of 10 mg/kg per day over a period of one month (Harries and Muller, 1969). This paper presents the conclusions of this study, together with an investigation of the use of a smaller dose of vitamin E which would be more suitable for therapeutic use.

Patients and Methods

Fifty children aged 6 months to 14½ years with CF were studied. None had evidence of liver disease and all were treated with moderate reduction in dietary fat together with pancreatic enzymes in the form of Pancrex V.‡ In addition vitamin supplements were given in the form of Abidec§ (contains no vitamin E).

Vitamin E was administered orally as DL- α -tocopheryl acetate¶ either as a fat-soluble preparation in tablet form (Ephynal), or as a clear water miscible preparation which contained a surface-active agent (Cremaphor EL, 16 g/100 ml) and glycerine.

Trial 1. We had previously (Harries and Muller, 1969) chosen 30 patients and randomly assigned them to 1 of 3 groups. 10 received no vitamin E supplement and served as a control group, 10 received the fat soluble preparation, and 10 children received the water miscible preparation. Both preparations were given as a

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‡ Pancrex V: Paines and Byrne Ltd.,

§ Abidec: Parke Davis and Co. Ltd., Each 0.6 ml contains: vitamin A, 5000 IU; vitamin B₆, 0.5 mg; vitamin D, 400 IU; nicotinamide, 5 mg; vitamin B₁, 1 mg; vitamin C, 50 mg. Dose 1 <yr = 0.3 ml/dy; >1 yr = 0.6 ml/dy.

¶ Roche Products Ltd.,

Results of Oral Administration of Two Preparations of Vitamin E

	Treatment Group	Serum Vitamin E (mg/100 ml)		
		Pre-treatment		
			1 mth	2 mth
Trial 1	Controls (no vitamin E)	0.22 ± 0.12 (10)	0.21 ± 0.14 (10)	0.76 ± 0.32
	Fat soluble preparation (10 mg/kg per day) ..	0.31 ± 0.13 (10)	0.79 ± 0.26* (9)	
	Water miscible preparation (10 mg/kg per day) ..	0.17 ± 0.08 (10)	1.36 ± 0.66* (8)	
Trial 2	Water miscible preparation (1 mg/kg per day) ..	0.27 ± 0.19 (10)		

Figures in parentheses denote number of children; *P for difference between means < 0.05 .

Mean serum vitamin E concentration in 22 children without malabsorption $0.80 \text{ mg}/100 \text{ ml} \pm 0.18$ (1 SD).

single dose of 10 mg/kg per day taken after breakfast for a total period of 1 month. Serum levels of vitamin E were determined before and at the end of this period and 1 month after discontinuing vitamin E.

Trial 2. Another 10 children received the water miscible preparation in a dose of 1 mg/kg per day taken as a single dose after breakfast for a period of 8 months. Serum levels of vitamin E were determined immediately before starting treatment, at intervals of 2 months during the treatment period, and at 2 and 4 months after discontinuing vitamin E.

In both trials a number of children failed to complete the planned period of treatment for a variety of reasons; the numbers in each group are given in the Table.

Serum vitamin E was measured in triplicate on aliquots of 0.3 ml serum by the method of Quaife, Scrimshaw, and Lowry (1949) with the following modifications. Bathophenanthroline was used as an indicator instead of alpha, alpha'-dipyridyl (Tsen, 1961); a correction was made for serum carotene by reading its extinction at $450 \text{ m}\mu$ (Bieri *et al.*, 1964); and orthophosphoric acid was added in order to minimize photo-reduction of ferric ions (Tsen, 1961).

Results

Trial 1. In the control group serum vitamin E remained unchanged, but in both treatment groups levels rose to within normal limits; the mean rise in serum vitamin E was significantly greater ($P < 0.05$) in the children who received the water miscible preparation.

Trial 2. The results are shown in the Table. The mean pretreatment concentration of serum vitamin E was similar to that in Trial 1; after 2 months of treatment the mean level had risen to $0.76 \text{ mg}/100 \text{ ml}$ which did not differ from the mean level achieved after 1 month of the fat soluble preparation in Trial 1. There was only a slight rise in serum levels during the remainder of the 8-month treatment period. After discontinuing treatment for 2 months the mean level had fallen

to $0.44 \text{ mg}/100 \text{ ml}$ and after 4 months to $0.32 \text{ mg}/100 \text{ ml}$; these values did not differ significantly from the pretreatment level of $0.27 \text{ mg}/100 \text{ ml}$.

Discussion

The higher mean levels of serum vitamin E achieved after 1 month of treatment with the water miscible preparation, compared with the fat soluble preparation in Trial 1, suggested that the former preparation was more efficiently absorbed. This confirmed the results of oral loading tests (Harries and Muller, 1969) and was further supported by the findings that the mean level of serum vitamin E after treatment for 2 months with the water miscible preparation in a dose of 1 mg/kg per day (Trial 2) was similar to that in the children who had received 10 times the dose of the fat soluble preparation (10 mg/kg per day) for one month.

It is suggested that the water miscible preparation is more efficiently absorbed because it is less dependent on the solubilizing properties of mixed micelles within the intestinal lumen. If this is so, then it is necessary to presuppose that micellar solubilization plays an important role in the luminal phase of vitamin E absorption. In the experimental animal, McMahon and Thompson (1969) found vitamin E to be better absorbed from a mixed micellar solution than from an emulsion, but Kelleher, Davies, and Losowsky (1969) were unable to detect any difference between its absorption from a suspension of Tween 80 or from an oily suspension. In normal young adults we have observed a water miscible preparation of vitamin E to be better absorbed than a fat-soluble one (Harries and Muller, unpublished), and similar findings are reported by Adam and Körner (1968). The precise mechanisms by which mixed micelles enhance absorption of such non-polar lipids as the fat soluble vitamins are not clear. It is likely that at least part of the function of mixed micelles is the

Tocopheryl Acetate to Children with Cystic Fibrosis

ml) Mean $\pm$ 1 SD

Starting Treatment			Time After Discontinuing Treatment		
4 mth	6 mth	8 mth	1 mth	2 mth	4 mth
0.71 $\pm$ 0.47 (7)	0.89 $\pm$ 0.55 (6)	0.84 $\pm$ 0.33 (6)	0.35 $\pm$ 0.10 (5) 0.400 $\pm$ 0.23 (4)	0.44 $\pm$ 0.23 (6)	0.32 $\pm$ 0.25 (6)

carriage of insoluble substances to their absorptive sites on the brush borders of epithelial cells (Mysels, 1969). Thereafter, there is probably a complex series of events, which controls the movement of substances across the membranes of the absorptive cell; for instance there is evidence that bile salts and several other detergents can affect the permeability of cell membranes and in this way could influence transfer of substances into cells (Gibaldi and Feldman, 1970).

Though medical literature during the past 30 years contains an abundance of reports concerning the clinical uses of vitamin E in man, the claims made in many of these reports remain uncorroborated. In recent years, however, a few careful and critical studies have stimulated a renewed interest in the possible role of vitamin E in the causation of human disease. Haemolytic anaemia (Oski and Barness, 1967) and subcutaneous oedema (Ritchie *et al.*, 1968) in premature babies, and reduced red blood survival in adults (Horwitt, Century, and Zeman, 1963) have been observed in vitamin E deficiency states. In children with abetalipoproteinaemia, preliminary findings have suggested a relation between the severe vitamin E deficiency which occurs in this condition and the retinal and neurological abnormalities that subsequently develop (Muller, Harries, and Lloyd, 1970). In children with CF, deposition of ceroid (Kerner and Goldbloom, 1960), focal muscle necrosis similar to that seen in animals with muscular dystrophy due to vitamin E deficiency (Oppenheimer, 1956), and creatinuria which was reversed by vitamin E therapy (Nitowsky, Gordon, and Tildon, 1956; Nitowsky *et al.*, 1962) have all been reported. It is doubtful, however, whether the high incidence of sterility found in males with CF is related to vitamin E deficiency (Kaplan *et al.*, 1968; Holsclaw and Schwachman, 1969).

Though the necessity for vitamin E therapy in CF remains unproven, it seems reasonable to

include it in the routine management of children with this condition. A total daily dose of 1 mg/kg per day of a water miscible preparation of α tocopheryl acetate can be anticipated to correct any pre-existing vitamin E deficiency after 2 months of starting treatment, and will thereafter maintain adequate serum levels. This dosage, however, does not apply to patients with liver involvement, whose requirements for vitamin E may be far greater, particularly when there is biliary obstruction (Muller and Harries, 1969).

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