Long-term oral vitamin E supplementation in cystic fibrosis patients: RRR-α-tocopherol compared with all-rac-α-tocopheryl acetate preparations

Brigitte M Winklhofer-Rooh, Martin A van 't Hof, and David H Shmerling

ABSTRACT To investigate the efficacy of three different vitamin E preparations for optimizing vitamin E status in cystic fibrosis (CF) patients long-term, 29 patients (aged 0.7–29.8 y) were randomly assigned to receive 400 IU of either RRR-α-tocopherol (A: 268 mg, n = 10) or all-rac-α-tocopherol acetate as a fat-soluble (B: 400 mg, n = 10) or water-miscible preparation (C: 400 mg, n = 9) and were followed for 6 wk. In the whole study group, plasma α-tocopherol concentrations increased from baseline (10.5 ± 4.6 μmol/L) to 3 wk (25.7 ± 6.5 μmol/L; P < 0.001), but not further between 3 and 6 wk; concentrations at 3 and 6 wk did not differ from those of age-matched control subjects (23.6 ± 3.9 μmol/L). There was no significant difference in the increase from baseline to 6 wk among preparations A (17.75 ± 8.43 μmol/L), B (14.0 ± 9.4 μmol/L), and C (15.5 ± 7.1 μmol/L). Because of differences in body weight, the dose administered ranged from 5.5 to 47.4 IU·kg⁻¹·d⁻¹; it correlated positively with the increase in plasma α-tocopherol concentrations (P < 0.001). There was no significant difference in the increase in plasma α-tocopherol concentrations between patients with CF-associated liver disease (n = 8) who received 10.2 ± 3.8 IU·kg⁻¹·d⁻¹ and those without liver disease taking comparable doses. We conclude that CF patients can be efficiently supplemented with 400 IU/d of any one of the three vitamin E preparations and plasma values of healthy control subjects can be achieved.

KEY WORDS All-rac-α-tocopheryl acetate, cystic fibrosis, liver disease, long-term supplementation, RRR-α-tocopherol, water-miscible vitamin E

INTRODUCTION

Cystic fibrosis (CF) patients, who in ~85–90% of cases have exocrine pancreatic insufficiency (1), frequently exhibit biochemical vitamin E deficiency even when taking pancreatic enzyme replacement therapy (2–4). Therefore, long-term oral supplementation has become part of the routine therapeutic regimen (5, 6). However, even though CF patients efficiently absorb a single oral dose of 100 mg all-rac-α-tocopheryl acetate/kg body wt (7, 8), 10–20% were shown to remain vitamin E deficient long-term (9, 10). In other studies, plasma α-tocopherol concentrations achieved in CF patients were not different from those of control subjects (2, 3, 11–13), but were considerably lower than plasma α-tocopherol concentrations published more recently for healthy individuals from different populations (14–16).

One decade ago the goal of vitamin E supplementation in CF patients was to prevent neurologic dysfunction, the clinical manifestation of vitamin E deficiency (3). Since then, evidence has accumulated that suboptimal vitamin E status is biologically relevant (17–20). Epidemiologic data document that plasma α-tocopherol concentrations of 26–28 μmol/L are associated with a decreased risk of mortality from ischemic heart disease (20), whereas lower concentrations, though still above the lower limit of normal, do not appear to exert a protective effect. In a comparison of two populations with plasma α-tocopherol concentrations of 25 ± 4 and 29 ± 5 μmol/L, the one with lower plasma α-tocopherol values showed significantly higher values for different indexes of lipid peroxidation (14). Supplementation with vitamin E in healthy subjects with baseline plasma α-tocopherol concentrations of 23 ± 4 μmol/L decreased susceptibility of low-density lipoprotein (LDL) to oxidative stress (15). Given the oxidant-antioxidant imbalance in favor of oxidation due to chronic lung inflammation on one hand, combined antioxidant deficiencies on the other (21), and evidence of increased oxidative damage (22), efficient antioxidant protection seems to be crucially important in CF patients. Biochemical vitamin E deficiency in CF patients is associated with impaired resistance of LDL to in vivo oxidative stress; improvement of vitamin E status fully reverses it to normal (16). There is preliminary evidence that optimization of antioxidant status might ameliorate chronic pulmonary inflammation in these patients (23). Supplementation with polyunsaturated fatty acids (PUFAs) is being considered to both correct biochemical essential fatty acid deficiency (with linoleic acid;...
24, 25) and reduce pulmonary inflammation (with n-3 fatty acids; 26, 27). This intervention may result in increased vitamin E demands, as suggested by a close inverse correlation between LDL resistance to oxidation and linoleic and arachidonic acid contents (16). Because of these new data, this study focuses on vitamin E supplementation in CF patients to achieve vitamin E status well above the lower limit of normal for healthy individuals of the same population.

SUBJECTS AND METHODS

Subjects

Thirty-one CF patients (18 males, 13 females) aged 0.7–29.8 y (median 6.9 y) with exocrine pancreatic insufficiency, who were under long-term care at our CF outpatient clinic and had plasma α-tocopherol concentrations below the 10th percentile of control subjects of the same age range (19.5 μmol/L) were enrolled. All took pancreatic enzymes—Prolipase (Cilag AG Pharma Schweiz, Schaffhausen, Switzerland), Creon (Kali-Duphar Pharma, Bern, Switzerland), and Panzytrat 25,000 (Knoll AG, Liestal, Switzerland)—in doses adjusted individually to the results of repeated fat-balance studies (28). The actual mean coefficient of fat absorption (CFA) was 81 ± 11%. Nine patients had been taking 100 IU (n = 4) or 200 IU (n = 5) daily of oral all-rac-α-tocopheryl acetate long-term before this study, but had not achieved normal vitamin E status. At study entry, patients were screened for the absence or presence of CF-associated liver disease (LD) by sonographic (hepatomegaly, grossly granular or nodular structure, portal hypertension, splenomegaly) and laboratory criteria (y-glutamyltransferase, alkaline phosphatase, total serum bile acids). Eight patients had LD on the basis of the following laboratory test results (median, range): y-glutamyltransferase activity (0.86, 0.27–2.86 µkat/L); alkaline phosphatase activity (14.49, 4.79–32.31 µkat/L); and total serum bile acid concentration (3.85, 0.42–8.2 µmol/L).

Twenty-nine control subjects (12 males, 17 females), matched with CF patients for age (± 3 mo), served as references for plasma α-tocopherol concentrations of patients after 6 wk of treatment. They were either attending the hospital for constitutional short stature, minor surgery, or ear, nose, and throat problems and were not taking drugs that affect fat or vitamin absorption, or they were healthy nonsmoking staff members who consumed an average diet and were not taking vitamin supplements. The study protocol was approved by the Ethics Committee of the Department of Pediatrics, University of Zurich, and informed consent was obtained from the patients or their parents.

Therapeutic intervention

Patients were randomly assigned to receive daily 400 IU (268 mg) RRR-α-tocopherol (preparation A, Multiben; Roche Pharma Schweiz, Reinach, Switzerland) or 400 IU (400 mg) all-rac-α-tocopheryl acetate, either in a fat-soluble (preparation B, Epyflan; F Hoffmann-La Roche AG, Basel, Switzerland) or water-miscible form (preparation C, E-Vimin; Astra Läkemedel AB, Södertälje, Sweden, which contains Polysorbate 80 as an emulsifier). This dose was chosen because long-term supplementation with 100–200 IU all-rac-α-tocopheryl acetate/d had not corrected low plasma α-tocopherol concentrations in a substantial proportion of CF patients before this study (unpublished data). Comparable doses on an IU/d basis were used to account for differences in biological activity between the RRR- and all-racemic form of α-tocopherol (see Appendix A). Preparations A and C were gelatin capsules and preparation B was a chewable tablet. Each capsule of preparation A contained 400 IU, whereas those of preparations B and C contained 100 IU of the vitamin; thus, patients took one capsule or tablet daily of preparation A and four of preparations B and C, respectively. Because the capsules and tablets could not be divided, dose administration was not adjusted to individual body weight. Body weight ranged from 8.4 to 72.9 kg; therefore, the dose per kilogram ranged from 5.5 to 47.7 IU · kg⁻¹ · d⁻¹.

Patients took the vitamin together with pancreatic enzymes at breakfast. Two infants had the content of the gelatin capsules placed into their mouths by their mothers. Compliance was monitored by asking patients and parents if any capsules had been missed and by checking the quantities of capsules supplied. All preparations were given to the patients in similar bottles and plasma samples from study patients were not indicated as such and were delivered to the laboratory together with those of patients not enrolled in the study. Measurement data were analyzed blind by using codes for the different preparations.

Assessment of treatment efficacy

The study protocol included three evaluations (study entry, and 3 and 6 wk) to provide information about the increase and a possible plateau effect in plasma α-tocopherol concentrations, and, in addition, in ratios of plasma α-tocopherol to cholesterol, while limiting the number of venipunctures to a minimum. Blood was drawn after an overnight fast and plasma was separated and kept at −20 °C for a maximum of 4 d before plasma α-tocopherol concentrations were determined by HPLC (29) in the laboratories of the Division of Vitamin Research of Hoffmann-La Roche. Plasma cholesterol concentrations were determined enzymatically with a kit from Beckman Ltd., Brea, CA. To correct for differences in plasma cholesterol concentrations among study patients and between patients and control subjects, ratios of plasma α-tocopherol to cholesterol were calculated (30).

Statistical analysis

Paired t tests were applied for comparison of plasma α-tocopherol concentrations in patients between baseline and 6 wk of treatment, two-sample t tests for comparisons between patients and age-matched control subjects, and between patients with and without LD. One-way analysis of variance (ANOVA) with Tukey’s range test was used for comparison of the increase in plasma α-tocopherol concentrations among the three preparation groups (with dose/kg included as a covariate) and of patient characteristics. Pearson’s correlation was applied for the relation between the increase in plasma α-tocopherol concentrations and the dose/kg body wt. STATGRAPHICS (version 6; STSC, Inc, Rockville, MD) was used for statistical procedures. Results are expressed as mean ± SD. Differences were considered significant at P < 0.05.
RESULTS

Study groups

Two patients dropped out because of noncompliance; 29 patients completed the study: 10 received preparation A, 10 preparation B, and 9 preparation C. Subject characteristics of the three groups are presented in Table 1. There were no significant differences in CFA or dose/kg body wt. Plasma cholesterol concentrations were lower in patients taking preparations B and C than in those taking preparation A (ANOVA, Tukey’s range test).

Treatment efficacy

Vitamin E was well-tolerated without evidence of any side effects. In the whole study patients plasma α-tocopherol concentrations increased between baseline and 3 wk, but not further between 3 and 6 wk (Table 2); at 6 wk they did not differ significantly from those of age-matched control subjects. Plasma α-tocopherol concentrations at 6 wk were below the 3rd percentile of control subjects (17.28 μmol/L) in three patients (10.8, 15.6, and 15.6 μmol/L), two of whom had had normal concentrations at 3 wk. Plasma α-tocopherol concentrations at 6 wk were above the 97th percentile of control subjects (30.0 μmol/L) in two patients (40.2 and 41.6 μmol/L). Ratios of plasma α-tocopherol to cholesterol increased accordingly and were significantly higher in patients at 6 wk than in control subjects (P < 0.0001) (Table 2). This can be explained by lower plasma cholesterol concentrations of patients compared with control subjects (P < 0.0001).

The increase in plasma α-tocopherol concentrations and ratios of plasma α-tocopherol to cholesterol from baseline to 6 wk did not differ among the three preparation groups (Table 3). There was a positive correlation between the increase in plasma α-tocopherol concentrations and the dose/kg body wt (P = 0.0006) (Figure 1), but dose/kg did not differ among the preparation groups.

Liver disease

Because there was a significant age difference between patients with and without LD (with LD: 14.5 ± 4.7 y; without LD: 8.4 ± 8.8 y) and, consequently, in body weight and dose/kg, further comparison between these two groups was performed only in patients receiving comparable doses/kg (n = 8 each, 10.2 ± 3.8 compared with 10.5 ± 4.4 IU · kg⁻¹ · d⁻¹).

The ratio of the number of patients taking preparations A:B:C was 3:3:2 in those with LD and 1:3:4 in those without. CFA (with LD: 79.6 ± 9.8%; without LD: 80.9 ± 12.6%) and plasma cholesterol concentrations (with LD: 3.60 ± 0.70 mmol/L; without LD: 3.31 ± 0.58 mmol/L) did not differ significantly between the two groups. There was no significant difference in the increase in plasma α-tocopherol concentrations and ratios of plasma α-tocopherol to cholesterol. Only ratios of plasma α-tocopherol to cholesterol at 6 wk (which were lower at baseline in patients with LD) remained lower in patients with LD compared with those without (Table 4).

DISCUSSION

As outlined above, we considered the overall goal of vitamin E supplementation in CF patients to be to achieve plasma α-tocopherol concentrations well above the lower limit of normal, and thus ensure efficient protection against free radical-induced tissue damage. Therefore, patients who had not reached plasma α-tocopherol concentrations above the 10th percentile of age-matched control subjects before this study were considered candidates for improvement of vitamin E status. After 3 wk of treatment, the vitamin E status of patients was comparable with that of the age-matched control subjects, which was also comparable with that of the general Swiss population (29). In contrast, healthy subjects from other populations had considerably lower plasma α-tocopherol concentrations (2-4, 31). A further increase was not observed between 3 and 6 wk, indicating that a steady state had been reached at or before 3 wk of treatment, which is compatible with plateaus reached between 3 d and 2 wk reported for healthy subjects (32–34). Three patients had plasma α-tocopherol concentrations below the 3rd percentile at 6 wk, two of whom had shown normal values at 3 wk; this most likely indicates a drop in compliance after 3 wk. The lack of a significant difference in

<table>
<thead>
<tr>
<th>Preparation</th>
<th>A, RRR-α-tocopherol (n = 6M, 4F)</th>
<th>B, fat-soluble (n = 6M, 4F)</th>
<th>C, water-miscible (n = 4M, 5F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>7.0 ± 6.9*</td>
<td>10.7 ± 7.9</td>
<td>12.8 ± 9.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>21.7 ± 14.4</td>
<td>34.0 ± 21.2</td>
<td>34.8 ± 20.8</td>
</tr>
<tr>
<td>CFA (%)</td>
<td>82.5 ± 11.0</td>
<td>83.8 ± 13.3</td>
<td>77.6 ± 8.2</td>
</tr>
<tr>
<td>Plasma cholesterol (mmol/L)</td>
<td>3.61 ± 1.3</td>
<td>3.31 ± 0.52*</td>
<td>3.14 ± 0.42*</td>
</tr>
<tr>
<td>Liver disease (n)</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Pretreated (n)</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Dose (IU · kg⁻¹ · d⁻¹)</td>
<td>25.5 ± 13.1*</td>
<td>17.3 ± 11.1*</td>
<td>17.5 ± 12.3*</td>
</tr>
<tr>
<td>(IU/d)</td>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>(mg/d)</td>
<td>268</td>
<td>400</td>
<td>400</td>
</tr>
</tbody>
</table>

* ± SD.

Coefficient of fat absorption.

Not significantly different among preparations (ANOVA, Tukey’s range test).

Significantly different from preparation A, P < 0.05 (ANOVA, Tukey’s range test).
TABLE 2
Response of the whole study group to 400 IU vitamin E/d and comparison of plasma values at 6 wk with those of age-matched control subjects from the same population.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 wk</td>
</tr>
<tr>
<td>Plasma α-tocopherol (µmol/L)</td>
<td>10.5 ± 4.6</td>
<td>25.7 ± 6.5</td>
</tr>
<tr>
<td>Ratio of plasma α-tocopherol to cholesterol (µmol/mol)</td>
<td>3.06 ± 1.30</td>
<td>7.93 ± 2.05</td>
</tr>
<tr>
<td>Plasma cholesterol (mmol/L)</td>
<td>3.47 ± 0.60</td>
<td>3.29 ± 0.57</td>
</tr>
</tbody>
</table>

1 ± SD; n = 29 subjects per group.
2 Significantly different from baseline, P < 0.0001 (paired t test).
3 Significantly different from patients at 6 wk, P < 0.0001 (two-sample t test).

the improvement of vitamin E status between patients with and without associated LD is in line with data of Stead et al (3), and suggests that the requirement of intraluminal bile acids for efficient vitamin E absorption was met in these patients.

To our knowledge, this is the first study showing a complete normalization of vitamin E status in CF patients, with plasma α-tocopherol concentrations of 26.2 ± 6.8 µmol/L. The importance of achieving plasma α-tocopherol concentrations this high is underlined by recent findings. In CF patients, median plasma α-tocopherol concentrations of 14.8 µmol/L were accompanied by increased lipid peroxidation (22); the increase in plasma α-tocopherol concentrations from 9.0 ± 4.2 to 27.8 ± 8.1 µmol/L (ratios of plasma α-tocopherol to cholesterol from 3.3 ± 1.8 to 9.9 ± 2.6 mmol/mol) was associated with a full reversion of impaired resistance to in vitro oxidative stress of PUFAs in LDL (16); only a further increase in plasma α-tocopherol concentrations from 28.3 ± 9.3 to 35.3 ± 9.5 µmol/L was associated with a decrease in lipid peroxidation (25). On the basis of the observation that increased susceptibility to peroxide-induced hemolysis occurs in CF patients with vitamin E status comparable with that of healthy control subjects of the same age range, James et al (31) proposed that a ratio of plasma α-tocopherol to cholesterol > 4.8 mmol/mol is necessary to protect against peroxidative damage.

TABLE 3
Effect of supplementation on plasma α-tocopherol concentrations and ratios of plasma α-tocopherol to cholesterol in the three groups.

<table>
<thead>
<tr>
<th>Preparation</th>
<th>A (n = 10)</th>
<th>B (n = 10)</th>
<th>C (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma α-tocopherol (µmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>10.7 ± 6.1</td>
<td>10.8 ± 4.9</td>
<td>9.9 ± 4.2</td>
</tr>
<tr>
<td>3 wk</td>
<td>27.8 ± 6.0</td>
<td>23.5 ± 7.1</td>
<td>25.6 ± 6.3</td>
</tr>
<tr>
<td>6 wk</td>
<td>28.4 ± 5.5</td>
<td>24.9 ± 8.4</td>
<td>25.4 ± 6.4</td>
</tr>
<tr>
<td>Increase from baseline to 6 wk</td>
<td>17.7 ± 8.4</td>
<td>14.0 ± 9.4</td>
<td>15.5 ± 7.1</td>
</tr>
<tr>
<td>Ratio of plasma α-tocopherol to cholesterol (µmol/mol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.89 ± 1.64</td>
<td>3.17 ± 1.16</td>
<td>3.13 ± 1.16</td>
</tr>
<tr>
<td>3 wk</td>
<td>7.97 ± 2.28</td>
<td>7.27 ± 1.94</td>
<td>8.61 ± 1.90</td>
</tr>
<tr>
<td>6 wk</td>
<td>7.88 ± 1.80</td>
<td>7.60 ± 1.58</td>
<td>8.31 ± 2.36</td>
</tr>
<tr>
<td>Increase from baseline to 6 wk</td>
<td>4.99 ± 1.49</td>
<td>4.43 ± 1.77</td>
<td>5.19 ± 2.38</td>
</tr>
</tbody>
</table>

1 ± SD. A, RRR-α-tocopherol; B, all-S-crac-α-tocopheryl acetate, fat-soluble; C, all-3Rα-tocopheryl acetate, water-miscible. There were no significant differences among groups for the increase from baseline to 6 wk for either measure (by ANOVA with Tukey’s range test).

The natural source of α-tocopherol, the RRR-enantiomer, is known to be a more biologically active form than the synthetic all-Rac-α-tocopherol. The relative activity of RRR-α-tocopherol is 1.36 times the activity of all-S-crac-α-tocopherol and 1.49 times that of all-3Rα-tocopheryl acetate, as derived from animal bioassays such as the resorplion-gestation test in rats (36). Even though this relation might be a function of bioavailability, it does not necessarily apply to humans. However, in a single-dose study in humans, the area under the concentration time curve from 0 to 96 h was 1.5-fold higher for RRR- than for all-S-crac-α-tocopherol (37). In previous studies (33, 38), and in the present investigation, this difference was taken into account by using comparable doses on an IU basis (see Appendix A).

All-S-crac-α-tocopherol is a mixture of eight stereoisomers, one-eighth of which is the RRR-form. Compared with the SRR-form, it is equally well absorbed but preferentially taken up by very-low-density lipoprotein (VLDL) and secreted into the plasma (39); a hepatic tocopherol-transfer protein is thought to be responsible for this selectivity (40, 41). One-half of the isomers from the all-S-crac-α-tocopherol preparation (with S-configuration at C2) are probably not recognized by the hepatic tocopherol-transfer protein. This is based on studies in humans receiving single pharmacologic doses of deuterated α-tocopherol (39, 40). From these studies, a rate of ~74 µmol/d was estimated for RRR-α-tocopherol resecretion into the plasma (42).

In this study, no differences were observed in the efficacy of 400 IU/d RRR- compared with the all-S-crac-α-tocopherol forms for increasing plasma α-tocopherol concentrations. This agrees with another long-term supplementation study that gave 800 IU (536

![FIGURE 1. The increase (Δ) in plasma α-tocopherol concentrations between baseline and 6 wk of supplementation is plotted against the daily dose/kg body wt. There was a significant correlation between dose/kg and the increase in plasma α-tocopherol concentrations.](image)
mg) RRR- and all-rac-α-tocopherol acetate (800 mg/d) to healthy subjects (33). In contrast, simultaneous ingestion of 150 mg/d of both deuterated RRR-α-tocopherol acetate (d3, 204 IU/d) and all-rac-α-tocopherol acetate (d6, 150 IU/d) over 11 d showed areas under the curve for plasma α-tocopherol concentrations almost twice as high for the RRR- as for the all-racenic form (43). Given a 50–80% fractional absorption of vitamin E in healthy subjects (44) and the average CFA of 83% in the study patients, it is very likely that < 50% was absorbed in this study. Nevertheless, the daily amount of RRR-α-tocopherol absorbed might have exceeded the capacity for resecretion into the plasma. It cannot be ruled out that a greater bioavailability of the RRR-form than that adjusted for with dosing on a IU basis is alleviated when high doses of the vitamin are given daily. On the other hand, simultaneous ingestion of two forms could result in competition for receptors, in contrast with ingestion of a single preparation.

Both preparations B and C were all-rac-α-tocopheryl acetate, an esterified form of α-tocopherol. Hydrolysis of the ester bond by pancreatic esterases is proposed to be important and rate-limiting, but may not be obligatory for absorption (45). CF patients may lack these esterases because of their exocrine pancreatic insufficiency, and it is uncertain if pancreatic enzyme supplements or esterases from enterocytes (45) compensate for this deficiency. The results of this study suggest that the ester bond was readily hydrolyzed because differences were not observed between the free and esterified α-tocopherol. This is in line with data on healthy subjects (46).

Water-miscible preparations contain an emulsifier to facilitate solubilization and enhance intestinal absorption in cases of fat malabsorption. Whereas in one study of CF patients equal doses (10 mg/kg) of water-miscible all-rac-α-tocopherol acetate led to higher plasma α-tocopherol concentrations than did fat-soluble all-rac-α-tocopherol acetate (12), no such difference was observed in this study. When doses in a 1:4 relation were given in another study (200 IU water-miscible preparation, not further specified, α-tocopherol acetate and 800 IU fat-soluble RRR-α-tocopherol acetate), no differences were seen, perhaps indicating greater bioavailability of the water-miscible preparation (13).

As noted, the dose given to individual patients was not adjusted to body weight in this study. A positive correlation between the increase in plasma α-tocopherol concentrations and the dose/kg was found in our study, in contrast with a lack of dose-response relation in healthy subjects in other studies who received doses as high as 440–1320 (32) or 1000–3000 IU/d (34). This relation did not affect the response to the three different preparations because dose/kg did not differ among the three groups. As can be seen in Figure 1, this correlation was not close enough to allow conclusions about the appropriate dose/kg for optimizing vitamin E status in virtually all CF patients. Recently, 5–10 IU (5–10 mg) all-rac-α-tocopherol acetate · kg⁻¹ · d⁻¹ did not correct vitamin E deficiency in 10% of infants with CF (9). In contrast, the authors of another study (3) concluded that CF patients, except those with severe LD, do not require > 10 mg all-rac-α-tocopherol acetate · kg⁻¹ · d⁻¹. However, after 1 mo with this dose, two of four of their patients with LD and two of four without LD still had plasma α-tocopherol concentrations below the 10th percentile of control subjects in the present study, as did three of four patients in both groups after 1–3 mo of 200 mg/d. In our study, all four patients without LD taking < 10 IU/kg (but a total of 400 IU/d) and four of five patients with LD taking a similar dose, achieved plasma α-tocopherol concentrations above the 10th percentile of control subjects, whereas other patients (with and without LD) taking > 10 IU/kg (but also a total of 400 IU/d) did not reach these concentrations. These data either confirm the well-known substantial inter-individual variability in the response to vitamin E intake in humans or reflect variable compliance.

In conclusion, to ensure optimal vitamin E status in practically all CF patients, we recommend supplementation with a daily dose of 400 IU, irrespective of the α-tocopherol preparation used. However, not all patients will require 400 IU/d. Even in view of the broad therapeutic range of vitamin E (47), preparations with different doses are needed to allow differentiated adjustment of the dose for the individual patient. This approach, however, requires patients to attend CF care centers where careful monitoring of treatment efficacy can be offered.

We acknowledge the determinations of plasma α-tocopherol concentrations in the laboratories of the Division of Vitamin Research of P. Hoffmann-La-Roche AG, Basel, Switzerland.

REFERENCES

LONG-TERM VITAMIN E SUPPLEMENTATION IN CF


43. Acuff RV, Thedford SS, Hildreth NW, Paps AM, Odom TA Jr. Relative bioavailability of RRR- and allrac-α-tocopherol acetate in


APPENDIX A

Vitamin E: form, activity, and mg substance

<table>
<thead>
<tr>
<th></th>
<th>IU/mg substance</th>
<th>Conversion from mg substance to mg α-TE</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRR-α-tocopherol</td>
<td>1.49</td>
<td>1.00</td>
</tr>
<tr>
<td>RRR-α-tocopheryl acetate</td>
<td>1.36</td>
<td>0.91</td>
</tr>
<tr>
<td>all-rac-α-tocopherol</td>
<td>1.10</td>
<td>0.74</td>
</tr>
<tr>
<td>all-rac-α-tocopheryl acetate</td>
<td>1.00</td>
<td>0.67</td>
</tr>
</tbody>
</table>

The international unit (IU) of vitamin E, which is numerically equal to the USP unit, is still used in labeling of vitamin E preparations, but should be replaced by mg substance and α-tocopherol equivalents (α-TE).