High doses of vitamin E in the treatment of disorders of the central nervous system in the aged1-3

Govind T Vatassery, Timothy Bauer, and Maurice Dysken

ABSTRACT Oxidative stress is a putative factor in the pathogenesis of many human disorders of the central nervous system. Therefore, antioxidants such as vitamin E have become attractive as therapeutic agents in the treatment of several diseases. In addition, vitamin E seems to play a specific role in the nervous system. As a result, vitamin E has been used in pharmacologic doses in the treatment of disorders such as Parkinson disease, Alzheimer disease, and tardive dyskinesia. One investigation showed that the use of 2000 IU all-rac-a-tocopheryl acetate is beneficial in the treatment of Alzheimergic disease. Similar doses of vitamin E, however, were not beneficial for delaying the progression of Parkinson disease. In other studies, dosages ≥400 IU vitamin E/d were found to be beneficial in the treatment of tardive dyskinesia, although this finding was not confirmed in a larger cooperative study conducted by the Veterans Administration. Even though the efficacy of vitamin E in the management of cardiovascular disease has been shown, the potential role of vitamin E in the treatment of cerebrovascular disease remains essentially unknown. The experience from 2 large clinical trials involving the oral intake of 2000 IU vitamin E/d suggests that vitamin E is relatively safe at this dosage for periods <2 y. However, the safety and efficacy of supplemental vitamin E over periods of many years in the prevention of neurologic diseases has not been adequately explored. Am J Clin Nutr 1999;70:793–801.

KEY WORDS Aged, elderly, antioxidants, central nervous system, megadose, therapeutic agent, a-tocopherol, vitamin E, Parkinson disease, Alzheimer disease, cardiovascular disease, tardive dyskinesia

INTRODUCTION Oxidative stress is a term describing the adverse effect of oxidative reactions induced by free radicals within biological organisms. Such stress has been implicated in the pathogenesis of various diseases affecting the human nervous system. Vitamin E is the only lipid-soluble, chain-breaking antioxidant in biological membranes (1, 2); hence, it is logical to propose that vitamin E may play a role in the treatment of some of those disorders in which oxidative stress has been implicated. Furthermore, many reports in the literature suggest that inadequate concentrations of vitamin E in the brain can lead to various deleterious neuro-pathologic changes (reviewed in reference 3). Several clinical trials have focused on the use of vitamin E in the treatment of disorders of the nervous system. The goal of this review is to examine the efficacy and safety of vitamin E in the treatment of a few selected disorders of the human nervous system in the aged.

NOMENCLATURE AND BIOLOGICAL ACTIVITY Vitamin E is the generic term for a group of compounds known as tocopherols and tocotrienols. α-Tocopherol has been shown to have the highest biological activity of all the tocopherols and tocotrienols and is the major vitamin E compound found in tissues of humans and animals. The tocopherol molecule, which has a saturated aliphatic side chain, can exhibit optical isomerism; the most common naturally occurring form is designated as the RRR- or d-α-tocopherol. The chemical structure of this form of vitamin E is shown in Figure 1. The 4 tocopherols are designated as α, β, γ, and δ depending on the number and position of methyl substituents on the benzene ring. Each of these molecules is also known to occur as a corresponding tocotrienol with 3 double bonds in the side chain. A brief historical introduction to the various forms of tocopherol and their synthesis can be found in an article by Horwitt (4).

The vitamin E activity of tocopherols is most frequently calculated in international units (IU), with 1 IU being defined as the biological activity of 1 mg all-rac-α-tocopheryl acetate. The relative biological activities of 1 mg of the most common forms of vitamin E are as follows: all-rac-α-tocopheryl acetate = 1 IU, all-rac-α-tocopherol = 1.10 IU, RRR-α-tocopherol = 1.36 IU, RRR-α-tocopherol = 1.49 IU, and RRR-γ-tocopherol = 0.15 IU (5).

Vitamin E is commercially manufactured as the acetate esters of RRR-α-tocopherol by using plant materials and as all-rac-α-tocopherol (dl-α-tocopherol) by chemical synthetic methods. The optically pure form or the RRR-α-tocopheryl acetate is often

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referred to as natural vitamin E and the all-rac- form as synthetic vitamin E. Many studies have examined the absorption and tissue retention of these 2 forms of vitamin E. Burton et al (6) studied plasma and tissue concentrations of α-tocopherol in humans after ingestion of either the RRR- or the all-rac- form of α-tocopheryl acetate. They found that the RRR- form had 2 times the available tocopherol of the all-rac- compound and proposed that the figure of 1.36 used for calculating biological activities be replaced by 2.

However, Weiser et al (7) reported that when rats were fed equivalent doses of the 2 types of tocopheryl acetates (using the ratio of 1.36:1), plasma and tissue α-tocopherol concentrations were equal. It is interesting to note that Weiser et al (7) also found that of the 8 optical isomers of α-tocopherol present in the all-rac-mixture, the four 2R isomers accounted for 70–86% of the tocopherol stereoisomers in tissues. This agrees with the results of many studies showing that the R configuration at the 2 position of the chromanol ring is the major determinant of biological activity (8). The preferential accumulation of the four 2R forms may account for the final activity ratio of RRR- to all-rac- of 1.36:1. Therefore, it is prudent to continue using this value (1.36) for the ratio of the bioavailabilities of the RRR- to all-rac- compounds.

In the 1980 and 1989 editions of Recommended Dietary Allowances (RDAs), the National Research Council suggests that vitamin E activity be expressed as RRR-α-tocopherol equivalents (α-TEs) (9). One α-TE is defined as the biological activity of 1 mg RRR-α-tocopherol. With use of the conversion figures provided in the RDA book, 1 IU is equal to 0.67 α-TE (9). We have used IU's in this report, however, for 2 reasons. First, IU’s are used much more widely than α-TEs for listing vitamin E doses in publications on vitamin E use in humans as well as on nutrition labels of consumer products such as vitamin pills. Second, the doses given in the text can be easily converted to α-TEs by multiplying by 0.67.

The contribution of γ-tocopherol as a source of vitamin E needs to be considered further. The richest sources of vitamin E in the US diet are vegetable oils such as soybean oil and corn oil, which contain more γ-tocopherol than α-tocopherol (9). As mentioned above, the biological activity of γ-tocopherol is only 15% of the activity of all-rac-α-tocopheryl acetate. None of the commercial preparations of vitamin E contain γ-tocopherol. Therefore, all clinical trials conducted so far have used only α-tocopherol. Both α- and γ-tocopherols are absorbed to the same extent, but the tissue availability of γ-tocopherol is much lower than that of α-tocopherol (10). Clement and Bourre (11) studied how different concentrations of RRR-γ-tocopherol added to a diet containing constant amounts of RRR-α-tocopherol affected the concentration of α-tocopherol in rat brains. They found that an increase in the γ-tocopherol content of the diet resulted in an increase in α-tocopherol in the forebrain, suggesting a positive interaction between γ- and α-tocopherols. Any clinical trial using a mixture of α- and γ-tocopherols will need to take such interactions into account.

**DOSAGES AND THEIR INFLUENCE ON TISSUE CONCENTRATIONS**

Various dosages of vitamin E have been used in clinical investigations in humans. Three levels of vitamin E intake can be distinguished: normal, supplemental, and pharmacologic. The RDA for vitamin E is 12–15 IU/d (9). Machlin (12) noted that the average intake of vitamin E is within the range of 4–22 IU/d and proposed that anything >30 IU/d be considered an elevated dosage. The current labeling regulations for foods from the Code of Federal Regulations establishes the reference daily intake for vitamin E as 30 IU (13). Following this guideline, most over-the-counter, one-a-day vitamin preparations contain 30 IU vitamin E. An unpublished analysis of the use of vitamin E in a population that was part of the third National Health and Nutrition Examination Survey showed that 44% of the population surveyed consumed 20–40 IU vitamin E/d (C Schweitzer and W Song, unpublished observations, 1999). According to these data, we propose that consumption of ≤40 IU/d be considered a normal intake (including the contribution from one-a-day type vitamins).

Millions of persons in this country (especially the elderly) take 200–400 IU vitamin E/d as a supplement. For example, Garry and Hunt (14) surveyed elderly subjects (60–93 y old, M: 72 y) in New Mexico and found that 56% of the men and 50% of the women consumed vitamin E pills; the average intake was 278 and 384 mg α-tocopherol for the men and women, respectively. Intake at the level of ≤400 IU can be termed supplemental vitamin E.

The various dosages of vitamin E used in clinical practice were summarized by Tanyel and Mancano (15). These dosages vary between 200 and 3600 IU/d in most cases with as much as 14000 IU/d prescribed in the special case of abetalipoproteinemia. Because 400 IU is a common daily dose used by many healthy humans, it would be appropriate to designate dosages >400 IU/d as pharmacologic doses or megadoses. Although somewhat arbitrary, this stratification does separate the dose schedules on the basis of the most frequent mode of intervention:

**FIGURE 1.** The chemical structure of the most active form of vitamin E: RRR-α-tocopherol or 2R,4′R,8′R-α-tocopherol. The compound is also referred to as d-α-tocopherol or natural vitamin E.
dietary intake, including one-a-day vitamin pills; vitamin E supplements; and pharmacologic vitamin E doses.

The relation between the dose of vitamin E given and the final tissue tocopherol concentration is complex, as summarized by Machlin (8). Using data from various studies, Machlin notes that tissue concentrations of tocopherol vary directly with the logarithm of the tocopherol dose used. Investigators using vitamin E as a therapeutic agent in nervous system disorders need to know the effect of oral vitamin E on vitamin E concentrations in the brain. Therefore, we conducted a study on the influence of high amounts of dietary vitamin E on brain concentrations of \( \alpha \)-tocopherol in rats (16). Male weanling rats were given 1000 IU all-rac-\( \alpha \)-tocopherol acetate/kg diet for 4 mo. At the end of this period, concentrations of \( \alpha \)-tocopherol in different regions of the brain had increased by 40% whereas concentrations in a peripheral tissue such as liver had increased 4.6-fold. Thus, there were considerable differences in the extent of loading of different tissues with \( \alpha \)-tocopherol. Because we used only one dietary amount of all-rac-\( \alpha \)-tocopherol acetate, we do not know whether the brain concentrations changed as a logarithm of the dietary dose. In any case, dietary ingestion of \( \alpha \)-tocopherol acetate does result in modest increases in brain concentrations of \( \alpha \)-tocopherol.

**EFFECTS OF VITAMIN E ON DISEASES OF THE NERVOUS SYSTEM**

It is well known that the nervous system undergoes neuropathologic changes if adequate concentrations of vitamin E are not present in the brain. Even though vitamin E deficiency is rare in humans, symptoms of vitamin E deficiency can occur in association with abetalipoproteinemia, chronic cholestatic hepatobiliary diseases, cystic fibrosis, and short-bowel syndrome (17). The neurologic disorder is characterized by cerebellar dysfunction and peripheral neuropathy and is manifested by areflexia, gait and limb ataxia, and decreased proprioception and vibration sense; administration of vitamin E results in considerable improvements in symptoms (17, 18). Even though these syndromes are important and are amenable to vitamin E treatment, this review will focus on disorders of the nervous system in the aged. First, however, we discuss the syndrome of ataxia with vitamin E deficiency (AVED). Although not associated with aging, AVED is of special theoretical significance.

A detailed study of the absorption and incorporation of \( \alpha \)-tocopherol into lipoproteins in subjects with AVED was first reported by Traber et al (19). Absorption of lipids is normal in AVED. Traber et al (19) found that all forms of tocopherol are transported in chylomicrons, but that the subsequent secretion of tocopherol into VLDL by the liver is fairly specific for \( \alpha \)-tocopherol. They hypothesized that this specificity may be due to the action of \( \alpha \)-tocopherol transfer protein in the liver and that AVED patients had a defective tocopherol transfer protein. Catignani and Bieri (20) reported previously the isolation of a tocopherol binding protein from rat liver. It has now been established that AVED is associated with specific mutations in the gene for the \( \alpha \)-tocopherol transfer protein (21). The authors found that this autosomal recessive form of ataxia maps to 8q13. A more detailed genetic analysis of the syndrome was reported by Cavalier et al (22), who found a total of 13 mutations in a study of 27 families. Further studies by Traber (23) showed that the \( \alpha \)-tocopherol transfer protein preferentially packages RRR-\( \alpha \)-tocopherol into nascent VLDL and is probably the major protein involved in the rapid recycling of \( \alpha \)-tocopherol in plasma. Clinically, AVED is similar to Friedrich ataxia, but head titubation and dystonia are found only in AVED (22). Investigations of AVED have improved our understanding of the handling of vitamin E by liver and blood plasma. The mechanism of the neurologic changes in AVED needs to be clarified by future work.

**PARKINSON DISEASE**

Considerable data suggest that excessive oxidative stress may be a causative factor in the development of Parkinson disease (3, 24, 25). Antioxidants such as vitamin E would be expected to protect against the development of Parkinson disease. This has been examined in several epidemiologic investigations. For example, in the Rotterdam Study, De Rijk et al (26) found that a high intake of vitamin E may be protective against the occurrence of Parkinson disease. A similar observation was made by Golbe et al (27) in a US population. However, Logroscino et al (28) found that there was no evidence of any association between Parkinson disease and antioxidant vitamins such as vitamin C and vitamin E. Thus, the results from the epidemiologic studies are not consistent in confirming a therapeutic role of antioxidants in Parkinson disease. Furthermore, investigations involving pharmacologic doses of vitamin E are more relevant to clinical practice. Hence, this review will focus primarily on the use of vitamin E as a therapeutic agent.

Vitamin E was used as a pharmacotherapeutic agent in the DATATOP (depenyl and tocopherol antioxidant therapy of Parkinson disease) investigation. In addition to vitamin E, this clinical trial involved the use of deprenyl (selegiline), an inhibitor of monoamine oxidase B, an enzyme that metabolizes monoamine neurotransmitters such as dopamine. When monoamine oxidase acts on dopamine, hydrogen peroxide is produced. Because hydrogen peroxide can cause peroxidative stress, especially in the presence of metal ions, it was hypothesized that monoamine oxidase inhibitors such as deprenyl would reduce the production of hydrogen peroxide and exert some antioxidant effects (29).

DATATOP was a double-blind, placebo-controlled study involving the use of 2000 IU vitamin E/d, 10 mg deprenyl/d, or both for the treatment of Parkinson disease (30). Between 1987 and 1988, 35 investigators from the United States and Canada enrolled 800 patients in this study. The subjects had untreated cases of Parkinson disease; the endpoint of the study was the time required for each patient to reach a stage when levodopa therapy had to be started. The initial results of the study prompted the authors to recommend the use of 10 mg selegiline/d as a viable therapeutic option for the early treatment of Parkinson disease; the investigation did not support the use of vitamin E in the treatment of Parkinson disease (30). The DATATOP experience was summarized recently by Shoulson et al (31). During the extended follow-up of 8.2 y, the clear-cut delay in disability of \( \approx \)9 mo observed with the use of deprenyl was not associated with longer life. This is consistent with the observation that the initial benefits of deprenyl were not sustained.

Note that Parkinson disease had already been diagnosed in the subjects in the DATATOP study; hence, > 80% of the neurons in these subjects’ substantia nigra had already degenerated (32). Vitamin E would be expected to have little effect on salvaging these neurons. DATATOP or other studies have not examined whether vitamin E may have a role in the prophylactic treatment.
of Parkinson disease. This issue can be addressed only after tests are available for a preclinical diagnosis of Parkinson disease.

Another important consideration is the length of vitamin E treatment needed to alter the course of the disease process. Recently, we studied the increases in concentration of α-tocopherol in the spinal fluid of 18 patients who consumed 2000 IU vitamin E/d and were randomly selected from the DATATOP study (33). The subjects had been taking vitamin E for various lengths of time (37–644 d). We found that treatment resulted in an average increase in spinal fluid α-tocopherol concentrations of 76 ± 10% (±SE). The net increases in spinal fluid α-tocopherol concentrations showed a significant, positive, linear correlation with the number of days of vitamin E ingestion. In other words, the data suggested that the α-tocopherol concentrations within the spinal fluid (and presumably in the brain) had not reached the highest values even after 644 d of treatment. This observation suggests that long-term treatment with vitamin E would tend to increase vitamin E concentrations within the brain and may increase the effectiveness of vitamin E as an antioxidant in neurodegenerative diseases. Fahn (34) reported the results of a long-term, open-label, pilot trial of high-dose vitamin E (3200 IU/d) along with 3000 mg vitamin C/d. The treatment, conducted over a period of 6–19 y, was effective in postponing the need for the use of levodopa by an average of 2.5 y in this group of 21 patients with early Parkinson disease.

The endpoint used in the DATATOP study was the time from random assignment until sufficient disability developed requiring treatment with levodopa (35). This is a quantifiable endpoint and is of great significance to the care of an individual with Parkinson disease. However, the endpoint is subject to influences other than motor performance. The use of a different endpoint focusing primarily or exclusively on motor performance could have changed some of the conclusions of the study.

ALZHEIMER DISEASE

Oxidative stress has also been suggested to be a causative factor in Alzheimer disease (36, 37). A study very similar to DATATOP was conducted by Sano et al (38). This was a 2-y, double-blind, placebo-controlled, randomized, multicenter clinical trial involving 341 patients with Alzheimer disease of moderate severity. Patients were given placebo, vitamin E (2000 IU/d), selegiline (10 mg/d), or a combination of vitamin E (2000 IU) and selegiline (10 mg/d). The 4 primary outcome measures were the time required for the occurrence of any of the following: death, institutionalization, loss of the ability to perform 2 of the 3 activities of daily living, and progression to severe dementia. The results were analyzed with and without use of the baseline score on the Mini-Mental State Examination as a covariate. When the data were adjusted for the baseline Mini-Mental State Examination scores, median survival increased significantly in the treated groups compared with the placebo group: the increase in median survival was 230 d in the vitamin E group, 215 d in the selegiline group, and 145 d in the group receiving both. No significant differences were found when the Mini-Mental State Examination was not used as a covariate. The authors concluded that treatment with α-tocopherol or selegiline slowed the progression of Alzheimer disease. Because α-tocopherol and selegiline delayed deterioration of function and thus the need for institutionalization, Sano et al suggested that treatment with these agents be considered in patients with Alzheimer disease.

Some of the problems of the study by Sano et al (38) were discussed in an accompanying editorial by Drachman and Leber (39). As pointed out in the editorial, Sano et al found that the treatment did not improve scores on the Mini-Mental State Examination or the cognitive portion of the Alzheimer’s Disease Assessment Scale. This raises the possibility that the treatment had only symptomatic effects and did not alter the progression of the disease. This criticism was also applied to the DATATOP study and was quite controversial at the time (40, 41). The editorial by Drachman and Leber also criticized the selection of the endpoints in the study by Sano et al, especially because death could occur for reasons totally unrelated to the advancement of the disease process. The fact that the results of the treatment with vitamin E were significant only after the covariate analysis was also considered a problem.

Like DATATOP, the study by Sano et al involved patients with the clinical manifestations of a neurodegenerative disease. It is doubtful whether antioxidants or any other agents could have regenerated the neurons that were irreversibly damaged before the disease became clinically manifest. The authors also pointed out later that their study did not examine whether prophylactic supplementation with vitamin E in appropriate populations, such as elderly persons at high risk of developing cognitive decline, would have a beneficial effect on memory (42). Furthermore, vitamin E treatment may be required for several years as discussed above. Hence, additional long-term studies are needed to test the effect of vitamin E in the prevention and treatment of Alzheimer disease and Parkinson disease involving patients at an early stage as possible.

CARDIOVASCULAR AND CEREBROVASCULAR DISEASE

Few, if any, investigations have examined the effect of supplemental or pharmacologic doses of vitamin E in human cerebrovascular disease. In contrast, several studies have focused on the effect of vitamin E in the prevention of cardiovascular disease. The lessons learned from these studies could be of great value in the management of cerebrovascular disease, including stroke. Obviously, these research findings are of great importance for the elderly; hence, we have included a discussion of vascular disease in general.

Results of numerous investigations suggest that oxidative modification of LDLs may play a critical role in atherogenesis (43). Antioxidants such as vitamin E would be expected to retard this pathologic process. One of the reports that involved large numbers of health professionals (39910 men and 87245 women) showed that intakes of vitamin E exceeding 100 IU/d were associated with lower risk of coronary heart disease in both men (44) and women (45). Jha et al (46) reviewed such epidemiologic reports as well as clinical trials and came to the conclusion that antioxidants, especially vitamin E, reduce the incidence of cardiovascular disease. In the epidemiologic studies, the relative risks for cardiovascular endpoints (fatal and nonfatal) were reduced by 31–65% after ingestion of supplemental vitamin E in humans. Interestingly, the supplementation had to last ≥2 y for the benefit to be apparent. The authors state that some of the randomized trials completed before 1995 did not show a protective effect of vitamin E, probably because the doses used were too small to have any effect. In the epidemiologic studies, vitamin C and β-carotene tended to be less beneficial than vitamin E.

The first large, double-blind study designed specifically to examine the effectiveness of vitamin E in preventing coronary
events was the Cambridge Heart Antioxidant Study (CHAOS) (47). This investigation involved 2002 patients with angiographically proven coronary atherosclerosis who were divided into 3 groups: 546 received 800 IU vitamin E, 489 received 400 IU, and 967 received placebo. There was an impressive 77% reduction in the risk of nonfatal myocardial infarction among those taking vitamin E. Steinberg (43) pointed out that these patients had advanced disease; therefore, the vitamin E treatment may not only have reduced lipoprotein oxidation but also affected lesion rupture, thrombotic tendency, or both.

Recently, it was recognized that inhibition of LDL oxidation may not be the sole reason for the effectiveness of vitamin E in altering the course of atherosclerosis. Steiner (48) noted that even though vitamin E is a potent inhibitor of platelet aggregation in vitro, it does not have this effect in vivo. However, platelet adhesion was inhibited by vitamin E in dosages of 400 IU/d. Similarly, vitamin E inhibited the adhesion of leukocytes to endothelium and promoted plaque stability, as reviewed by Dzau et al (49). In addition, α-tocopherol inhibited smooth muscle cell proliferation (50). In this case, α-tocopherol inhibited protein kinase C and smooth muscle cell proliferation along with activating protein phosphatase in a dose-dependent manner. Thus, vitamin E may have several effects on preserving the optimal function of the vasculature. For a more complete discussion of vitamin E and atherosclerosis, the reader is referred to an excellent review by Chan (51).

At least 6 prospective clinical trials involving vitamin E in dosages >300 IU/d are being conducted at this time [listed by Jha et al (46)]. Among these prospective studies, some initial results from CHAOS have been published, as discussed above. It is unfortunate that only one of the current investigations deals with a healthy population; the rest involve subject populations with some form of cardiovascular disease. In any case, the results from these studies will provide additional data on the effectiveness of vitamin E in preventing cardiovascular incidents. Most of the studies being conducted are also monitoring the incidence of stroke among their subjects. Hence, data on the effect of vitamin E on cerebrovascular incidents will be forthcoming.

TARDIVE DYSKINESIA

Tardive dyskinesia is a movement disorder that occurs as a side effect of the chronic administration of neuroleptic medications for control of psychotic disorders. It is characterized by abnormal movements in the orofacial region as well as choreoathetoid movements of the extremities and trunk. The incidence of tardive dyskinesia is estimated to be 19% after 4 y of treatment with neuroleptic drugs and 40% after 8 y (52). Interestingly, the prevalence of tardive dyskinesia has been reported to increase to 50–70% in patients aged >65 y (52). The mechanism underlying the development of these abnormal movements is still unclear. One of the most popular hypotheses is that blockade of postsynaptic dopamine receptors results in supersensitivity of these receptors in basal ganglia and that the movement disorder occurs as a result. Some of the shortcomings of this hypothesis are as follows (53): 1) the increase in dopamine binding sites occurs within days of treatment, whereas tardive dyskinesia develops after several months to years; 2) the receptor numbers return to normal quickly after cessation of neuroleptic treatment, whereas the dyskinesia persists much longer; and 3) other neurotransmitter systems in addition to dopamine, such as γ-aminobutyric acid, are also involved in the disorder. Therefore, some investigators have proposed that the increased production of oxygen free radicals and other toxic metabolites during neuroleptic treatment may be involved in the degeneration of dopaminergic as well as other neurotransmitter systems and that free radical–induced damage may be a common mechanism for the production of tardive dyskinesia (54). A logical extension of this postulate is that antioxidants such as vitamin E that can neutralize free radicals may be effective in the treatment of tardive dyskinesia.

At least 12 studies on the use of vitamin E in treating tardive dyskinesia were performed before 1996 and were reviewed by Lohr and Caligiuri (55). None of the 12 studies reported some improvement with vitamin E in at least a portion of the study subjects; improvements in scores on the abnormal involuntary movement scale ranged from 18% to 47%. The dosages of vitamin E used were from 1200 to 1600 IU/d for periods of 4 wk to a few months. The Lohr and Caligiuri investigation itself (55) was a double-blind, placebo-controlled clinical trial of 800 IU vitamin E twice daily with 18 subjects assigned to placebo and 17 to the treatment group. The study lasted for 2 mo. Significant improvements were seen in scores on the abnormal involuntary movement scale of the subjects taking vitamin E. One of the consistent observations in this and some of the earlier reports is that subjects who had tardive dyskinesia for shorter periods of time (<5 y) tended to do better with vitamin E treatment. Note that all of the studies reported so far have been of short duration, lasting at most a few months. Also, no studies have evaluated the potential ability of vitamin E to prevent the incidence of tardive dyskinesia.

The Department of Veterans Affairs completed a cooperative study involving 9 sites that tested the effectiveness of vitamin E in the treatment of tardive dyskinesia. Recently, Adler et al (56) published the results of one of the pilot studies completed before the cooperative study. These authors found a highly significant reduction in the severity of tardive dyskinesia in the vitamin E–treated group compared with the placebo group. However, this effect of vitamin E treatment was not observed in the larger cooperative study. Even though the details have yet to be published, this lack of therapeutic effect of vitamin E was summarized in an editorial (57) in which the authors pointed out that tardive dyskinesia decreased in both the vitamin E and placebo groups. This editorial also stated that the cooperative study was designed to enroll only patients who had tardive dyskinesia for <5 y, but that this criterion was abandoned because of a lack of availability of subjects for study. Another possible reason for the lack of effect of vitamin E in the larger cooperative study could be that patients with a more refractory form of tardive dyskinesia were enrolled in the investigation. Furthermore, as mentioned in the editorial, the dosages of antipsychotic drugs used were gradually reduced and a dramatic switch to atypical antipsychotic agents was made during the time the cooperative study was conducted. Therefore, it is still likely that certain types of tardive dyskinesia may be amenable to treatment with vitamin E.

SAFETY OF VITAMIN E

The investigations discussed above suggest that consumption of supplemental amounts of vitamin E over long periods of time may be useful in the treatment of certain human maladies. Hence, the safety of consuming large doses of vitamin E is of great interest. This subject was reviewed by Bendich and Machlin (38), who stated that animals tolerate doses as high as 1 g/kg body wt.
Ataxia with vitamin E deficiency

RRR-α-Tocopherol, 150 mg/kg body wt

Unusually high dose is used because malabsorption and lipid abnormalities make absorption and transfer into central nervous system difficult (22).

Ataxia with vitamin E deficiency

RRR-α-Tocopherol, 800 mg twice daily

Rare familial disease caused by mutations in the α-tocopherol transfer protein gene (22).

Cystic fibrosis

all-rac-α-Tocopheryl acetate, 5–10 IU · kg⁻¹ · d⁻¹

Sokol (17).

Short-bowel syndrome

all-rac-α-Tocopheryl acetate, 200–3600 IU/d

Sokol (17).

Selected human diseases for which vitamin E has been used as an oral therapeutic agent

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<tr>
<th>Condition</th>
<th>Dosage</th>
<th>Remarks and references</th>
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<tbody>
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<td>Alzheimer disease</td>
<td>all-rac-α-Tocopheryl acetate, 2000 IU/d</td>
<td>Sano et al (38). A larger clinical trial is underway.</td>
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<tr>
<td>Tardive dyskinesia</td>
<td>all-rac-α-Tocopheryl acetate, 400 IU/d</td>
<td>Adler et al (56). A larger cooperative study did not confirm this effect (57). Higher dosages have also been used (see text).</td>
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<td>Abetalipoproteinemia</td>
<td>RRR-α-Tocopherol</td>
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<td>Abetalipoproteinemia</td>
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<tr>
<td>Cystic fibrosis</td>
<td>all-rac-α-Tocopheryl acetate, 5–10 IU · kg⁻¹ · d⁻¹</td>
<td>Sokol (17).</td>
</tr>
<tr>
<td>Short-bowel syndrome</td>
<td>all-rac-α-Tocopheryl acetate, 200–3600 IU/d</td>
<td>Sokol (17).</td>
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Human clinical trials have involved dosages as high as 3200 IU/d. Even though supplemental vitamin E is being consumed by large portions of the US population, reports linking vitamin E to any type of toxic effects have not appeared in the literature. It is important to stress, however, that there have been few studies of the safety of vitamin E supplements over long periods of time. Meydani et al (59) studied the effect of the ingestion of 800 IU vitamin E/d for 4 mo in healthy subjects aged >65 y. Vitamin E consumption did not alter results on any of the tests of hepatic or renal function, hematologic status, plasma lipid or lipoprotein concentrations, bleeding time, serum autoantibody concentrations, or the ability of neutrophils to kill Candida albicans. Diplock (60) reviewed 10 clinical studies conducted before 1989 and concluded that ingestion of vitamin E at dosages of 100–3200 IU/d for periods of 4 wk to a few months was not associated with any adverse effects. Additionally, human subjects were given 2000 IU vitamin E/d for periods up to 36 mo in the DATATOP study without adverse effects (61). The study by Sano et al (38) confirms this observation. These reports indicate that vitamin E can be used by humans in fairly large doses. However, data on the effect of pharmacologic doses of vitamin E in humans over very long periods of time are still not available.

Adverse reactions from consumption of high amounts of vitamin E have been reported mainly in subjects with suboptimal vitamin K status. A brief historical account of the interaction between vitamin E and vitamin K is provided by Nelson (62). This author reports that in a phase 1 trial of intravenous vitamin E in patients with neuroblastoma, 2 patients exhibited bleeding diathesis with increases in prothrombin time and corresponding decreases in factors VII, IX, and X. It was also found that infusing menadione sodium diphosphate before the ingestion of vitamin E prevented these effects on coagulation. Other studies in human subjects show that the reductions in vitamin K–dependent coagulation factors II, VII, IX, and X induced by treatment with warfarin were further enhanced by administration of vitamin E (63). It has been proposed that vitamin E quinone (an oxidation product of vitamin E) interferes with the carboxylase reaction that uses vitamin K as a cofactor and converts several of the coagulation factors to their active forms (63, 64). These changes are readily reversed by administration of vitamin K. Therefore, it would be prudent to monitor coagulation function (eg, prothrombin time) in persons with potential vitamin K deficiency, persons undergoing anticoagulant therapy, or persons with coagulopathy if these subjects are consuming supplemental or pharmacologic doses of vitamin E.

A report on the use of vitamin E, vitamin A, or both in retinitis pigmentosa is also of interest (65). This was a randomized, double-blind, placebo-controlled trial of the treatment of retinitis pigmentosa with 15 000 IU vitamin A, 400 IU vitamin E, or a combination of both. In this study, vitamin E use was associated with a greater decline in cone electroretinogram amplitude than was treatment with vitamin A or placebo. The authors cautioned against the use of supplemental vitamin E in these patients and suggested that vitamin E interferes with the absorption of vitamin A. It is well known that biochemical interactions exist between vitamin A and vitamin E. For example, vitamin E reduces the rate of hydrolysis of retinyl esters in the liver (66). The study by Berson et al (65) has been criticized for various reasons, however. For example, an editorial in Archives of Ophthalmology pointed out that no changes in global visual function (visual field area or visual acuity) were seen in any of the treatment groups (67). The situation is complicated further by more recent observations. Yakota et al (68) described a new syndrome of Friedrich-like ataxia and retinitis pigmentosa caused by a defect in the α-tocopherol transfer protein gene in 4 unrelated Japanese subjects. The oral administration of vitamin E appeared to halt the progression of the visual and neurologic symptoms in these subjects. Furthermore, vitamin E deficiency in animals is also known to cause changes similar to retinitis pigmentosa (69). Thus, it is possible that vitamin E has a role in the treatment of some forms of retinitis pigmentosa and this issue needs to be investigated further. Even though the study by Berson et al (65) suggested that vitamin E may have some deleterious effects in patients with retinitis pigmentosa, this has not been confirmed so far.

Examination of some of the clinical conditions in which vitamin E has been used as a therapeutic agent shows that various doses have been used for various lengths of time. Some of the results are summarized in Table 1. Of the diseases listed in this table, the use of vitamin E in Alzheimer disease and tardive dyskinesia awaits additional confirmation.

MECHANISM OF ACTION OF VITAMIN E

The most widely accepted role for vitamin E is that of a general lipid antioxidant. In fact, vitamin E is the major chain-breaking antioxidant present in biological membranes (1, 2). Hence, it is not surprising that vitamin E deficiency produces several pathologic changes involving many organs in experimental animals (70). Numerous studies have been done to elucidate the mechanism of action of vitamin E in the brain. Our own studies show that vitamin E...
may play a special role in the cerebellum because concentrations of vitamin E are the lowest in this part of the brain and vitamin E is depleted faster from the cerebellum than from other parts of the brain during vitamin E deficiency (3, 71). Neuroaxonal dystrophy is a neuropathologic hallmark of vitamin E deficiency in rodents as well as in primates (72, 73). Swelling and accumulation of organelles at distal ends of nerves are usually observed (74). The following are some selected changes associated with vitamin E deficiency in the brain. 1) Electrophysiologic investigations in humans under vitamin E deficiency conditions show signs of a distal “dying-back” axonal neuropathy, especially in the posterior columns and the gracile and cuneate nuclei (75). 2) The induction of long-term potentiation by tetanic stimulation in hippocampal slices is impaired in vitamin E deficiency (76). 3) A morphometric investigation of the synaptic junctions in the cerebellar glomeruli showed that the number and average size of the synapses were significantly reduced as a result of vitamin E deficiency in rats (77). 4) Vitamin E has been shown to protect neurons from the toxic effects of various compounds; eg, hypothalamic β-endorphin neurons were protected from estradiol-induced neurotoxicity (78). 5) Prostaglandin synthesis in the brain was altered as shown by a decrease in prostaglandin E2 production in brain homogenates from vitamin E–deficient rats (79). 6) Cytosolic phospholipase A2 activity was reduced in the cerebellum of vitamin E–deficient chicks (80).

Work on peripheral tissues such as muscle indicates that vitamin E may also be involved in the signal-transduction pathway. Azzi et al (81) found that vitamin E is an inhibitor of protein kinase C and ultimately leads to the inhibition of proliferation of smooth muscle cells. RRR-α-Tocopherol seems to be the most active tocopherol in this biological role of vitamin E. More recent work from this group shows that only the α form of protein kinase C is inhibited by α-tocopherol and that the inhibition is linked to the activation of a protein phosphatase, which in turn dephosphorylates the kinase and inhibits the activity (82). Thus, the available data suggest that vitamin E may have several functional roles associated with membranes. However, a specific and unique mode of action of vitamin E remains an elusive concept.

CONCLUSIONS

The popular press is full of claims about the efficacy of vitamin E in both ameliorating various diseases and enhancing the quality of human life. Several of these claims are without any foundation and can easily be dismissed. The professional community needs to be ever vigilant about scrutinizing such claims by using available scientific information. The DATATOP study found that pharmacologic doses of vitamin E were not effective in the treatment of Parkinson disease whereas vitamin E treatment has shown promise in the management of Alzheimer disease and tardive dyskinesia. Even though further studies are needed to establish the use of vitamin E in these conditions, vitamin E in dosages of 2000 IU/d can be recommended for patients with Alzheimer disease. Use of vitamin E in dosages of 1200 IU/d can be suggested for the treatment of tardive dyskinesia. The lower dosage is being recommended for tardive dyskinesia because several studies reported improvement in clinical disability at even lower dosages. Such treatment is relatively safe (58, 83) and the monthly cost is low. The primary contraindication for the use of vitamin E is the existence of changes in coagulation indexes induced by warfarin-type drugs. Even under these conditions, however, ensuring an adequate supply of vitamin K seems to forestall any potential complications. Nonetheless, it would be prudent to monitor the status of blood coagulation indexes for absolute safety.

One of the lessons learned from the clinical trials performed to date is that the earlier vitamin E treatment is started in the course of the disease, the better the outcome. It would indeed be of great interest to try vitamin E treatment immediately after a preclinical diagnosis of a disorder. Unfortunately, preclinical diagnostic tests are not currently available for most of the neurodegenerative diseases.

It is likely that treatment with vitamin E may need to be continued for years before efficacy can be definitely established. In a viewpoint article on the use of antioxidants in atherosclerosis, Steinberg (84) suggested that even a 5-y study may be too short for establishing the efficacy of antioxidants. Of course, a long-term study could be shortened midstream if the results were positive. As discussed above, our own data from samples in the DATATOP study show that the net increases in spinal fluid vitamin E after ingestion of the compound had not reached equilibrium even after 20 mo (33). Thus, longer durations of treatment may be essential for attaining therapeutic concentrations of vitamin E in the spinal fluid and brain.

It is well known that antioxidants have biological interactions with one another. Use of antioxidant combinations such as vitamin E and vitamin C or the combination of antioxidants with standard therapies may offer additional benefits to patients. More clinical trials involving combinations of these agents need to be conducted.

Finally, the difficulties of evaluating a nutrient in the treatment or prevention of human diseases need to be kept in mind. In an editorial in the New England Journal of Medicine, Angell and Kassirer (85) pointed out that papers in medical journals are working papers rather than distilled wisdom. Thus, one should expect to see controversial results. It should not come as a surprise when one paper in which antioxidants are reported to reduce the risk of developing a disease is followed by another that refutes this finding. Block (86) has also highlighted some of the limitations of clinical trials. These trials are of necessity limited in the number of agents that can be tested, the time of trial, and the number of dosages that can be used. Epidemiologic and clinical trials form small parts of the puzzle and these have to be integrated into the final solution over time and after many different investigations. So far, numerous reports in the literature show that vitamin E has a unique role to play in the function of the nervous system. This suggests that it is likely that some disorders of the nervous system may be particularly amenable to treatment with vitamin E.

Considerable volumes of information needed to be amassed before the professional community accepted the importance of a reduction in blood cholesterol concentrations in reducing the incidence of atherosclerosis. The potential benefits of vitamin E in the treatment and prevention of the diseases mentioned above may come only after we have accumulated many positive results. It is fortunate that many experimental and clinical trials are underway: the situation should be much clearer soon.

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