Clinical Uses and Abuses of Vitamin E in Children (43432)

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Abstract. **The major benefits arising from elevated dosages of vitamin E have been the relief of symptoms of vitamin E deficiency in humans with abetalipoproteinemia and chronic cholestasis. In addition, supplements of vitamin E prevent the isolated vitamin E deficiency that has recently been associated with spinocerebellar symptoms.**

In keeping with the view that newborn infants, and especially premature infants, suffer from vitamin E deficiency, elevated dosages of vitamin E have been administered to prevent the anemia of premature infants, retrolental fibroplasia, bronchopulmonary dysplasia, and intraventricular hemorrhage. However, the results have been conflicting. Furthermore, some infants treated with vitamin E die unexpectedly.

The life-threatening hazard of such treatments has been attributed mainly to polysorbates that are used as detergents in preparations of vitamin E for intravenous use rather than to vitamin E itself. The possibility that vitamin E, in its action as an antioxidant, inhibits the generation of superoxide anion in leukocytes is examined in this paper. [P.S.E.B.M. 1992, Vol 200]

Benefit in Clinical Use of Vitamin E. Previously, it was generally thought that vitamin E, even when administered in large amounts, was essentially nontoxic. Thus, elevated dosages of vitamin E were used successfully to treat vitamin E deficiency in humans that was associated either with abetalipoproteinemia and fat malabsorption caused by cholestasis or with a specific reduction in the vitamin E content of nervous tissues without fat malabsorption. Spinocerebellar neurological symptoms and retinal lesions result, including areflexia, truncal and limb ataxia, sensory neuropathy, ophthalmoplegia, and retinopathy (1). Large doses of vitamin E either prevent or arrest the clinical manifestations. In chronic cholestasis, the symptoms of vitamin E deficiency appear at a relatively early age, whereas in abetalipoproteinemia, clinical manifestations develop more gradually (Table I). Thus, it has been proposed that correction of vitamin E deficiency in children with both diseases within the first several years of life will completely prevent or reverse the neurological dysfunction. In contrast, delaying therapy may result in irreversible neurological damage.

More recently, vitamin E deficiency without evidence of fat malabsorption has been reported in association with spinocerebellar degeneration. In these patients, who show no defect in gastrointestinal function, no liver dysfunction, or, in fact, any metabolic abnormalities, the progression of the disease is halted by vitamin E therapy. The disease has been termed isolated vitamin E deficiency. The reports are summarized in Table II. In patients, the condition seems to be inherited as an autosomal recessive trait (2, 3).

Whether or not the use of elevated dosages of vitamin E should be recommended for certain diseases in premature infants is controversial. Previously, newborn infants, and especially premature infants, were thought to suffer from vitamin E deficiency because of their low plasma vitamin E levels and the high susceptibility of their red blood cells to lysis by hydrogen peroxide (Fig. 1).

Furthermore, vitamin E deficiency has been implicated in four neonatal conditions: anemia of premature infants, retrolental fibroplasia, bronchopulmonary dysplasia, and intraventricular hemorrhage. A hemolytic anemia associated with thrombocytosis, eczema, and edema has been reported in a minority of preterm infants, who were given high amounts of polyunsaturated fatty acids in their formulas. These infants responded to vitamin E therapy. However, the prophylactic use of an elevated dosage of vitamin E to prevent

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anemia in premature infants is controversial (4). There is no evidence for beneficial effects of vitamin E in bronchopulmonary dysplasia. In addition, the prophylactic use of pharmacological dosages of vitamin E for prevention of retrolental fibroplasia and intraventricular hemorrhage is not well accepted (5–8).

Hazards in the Use of Large Doses of Vitamin E

As the use of daily elevated dosages of oral, intramuscular or intravenous preparations of vitamin E to very low birth weight infants has increased for the possible prevention of a variety of vitamin E-responsive diseases, some treated infants have died unexpectedly, some have shown an increased frequency of necrotizing enterocolitis and sepsis, and some have developed an unusual set of symptoms, including hepatic, pulmonary, and renal injuries. This set of symptoms has been called the E-Ferol syndrome (9). Within 6 months, approximately 40 premature infants died after receiving the E-Ferol preparation. Thus, in 1984, the Committee on the Fetus and Newborn of the American Academy of Pediatrics recommended that high doses of vitamin E should not be routinely given to very low birth weight infants, and that the intravenous preparation should be withdrawn from the market (10). Fortunately, there have been no vitamin E preparations for intravenous use in Japan. However, an intramuscular preparation was used in some newborn infants kept in certain nurseries in Japan (11). The large intramuscular dosages of vitamin E induced an increased frequency of sepsis but not of necrotizing enterocolitis in Japanese infants (Table III).

The E-Ferol preparation includes the polysorbates, Tween 80 and Tween 20, to emulsify vitamin E. The toxicity of this preparation has been attributed by most workers to its polysorbate vehicle rather than to vitamin E itself (12).

Table I. Vitamin E Deficiency in Abetalipoproteinemia and in Fat Malabsorption with Cholestasis

	Abetalipoproteinemia	Fat malabsorption cholestasis
Areflexia	30% symptomatic at 10 yr	50% symptomatic at 1–3 yr
Ataxia and neuropathy	All at 20 yr	Majority at 3–6 yr
	Severe neuromuscular disabling by 8–10 yr	No spontaneous improvement

Superoxide Production and Vitamin E Level in Leukocytes

The most elevated serum vitamin E concentration, observed in response to pharmacological dosages, was reported to be 12.9 mg/dl, which is more than 10 times higher than the normal adult level (9). With regard to the clinical use of vitamin E in treating the above-cited diseases in premature infants, the therapeutically effective serum vitamin E concentration is expected to be

Table II. Vitamin E Therapy in Patients with Isolated Vitamin E Deficiency (3)

Author	Date	Patient		Family history	Daily dose of vitamin E[a]	Duration of therapy	Response to vitamin E therapy
		Sex	Age of onset				
Burk	1981	M	12	Yes	1.5 g	12 mo	Clinical improvement
Laplante	1984	M	10	?	NA[b]	NA[b]	Clinical improvement
Harding	1985	F	23	Yes	2.0 g	2 wk	Normal serum level
					0.8 g	15 mo	No further progress
Krendel	1987	M	19	Yes	1800 IU	6 wk	No worsening, but no objective improvement
Stumpf	1987	F	16	No	2.0 g	2 wk	Normal serum level
					0.8 g	6 mo	No clinical change
Yokota	1987	M	57	Yes	800 IU	7 mo	Normal serum level Slight improvement
Sokol	1988	F	11	Yes	800 IU	18 mo	Clinical improvement
		M	27	Yes	800 IU	20 mo	No symptoms unless no changed vibratory sensation
		F	3–4	No	2000 IU	16 mo	No dysarthria
					800 IU	+20 mo	No head titubation

[a] 1 IU of vitamin E = 1 mg *all-rac*-(DL)-α-tocopheryl acetate = 0.67 mg *RRR*α-tocopherol.
[b] NA, not available.

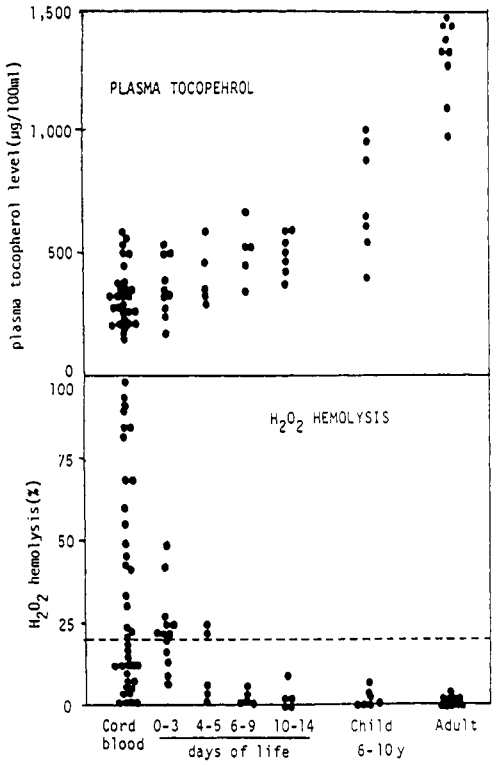

Figure 1. Plasma tocopherol levels and hydrogen peroxide hemolysis in relation to age.

Table III. Vitamin Therapy in Neonates and Infectious Diseases (11)

Dosages	No infections	Infectious diseases		Percentage with infection
		All	Sepsis	
Intramuscularly				
None	48	11	3	19
<40 mg/kg	19	8	2	30
>40 mg/kg	14	17[a]	12[a]	55
By mouth				
None	48	11	3	19
<20 mg/kg/day	10	2	1	17
50 mg/kg/day	12	4	0	25
100 mg/kg/day	14	2	0	13

[a] $P < 0.01$.

more than 3 mg/dl, which is approximately three times higher than the adult level (9).

The superoxide anion produced in leukocytes is an oxygen radical important for bacterial killing. Because vitamin E is an antioxidant, the bacterial killing mechanism in leukocytes might well be inhibited by large doses of vitamin E. Engle (13) recently reported that a tocopherol level of more than 5 mg/dl in the medium significantly inhibits the *in vitro* production of superoxide anion in polymorphonuclear cells (PMN). Thus, pharmacologic serum levels of vitamin E might predispose premature infants to infectious complications,

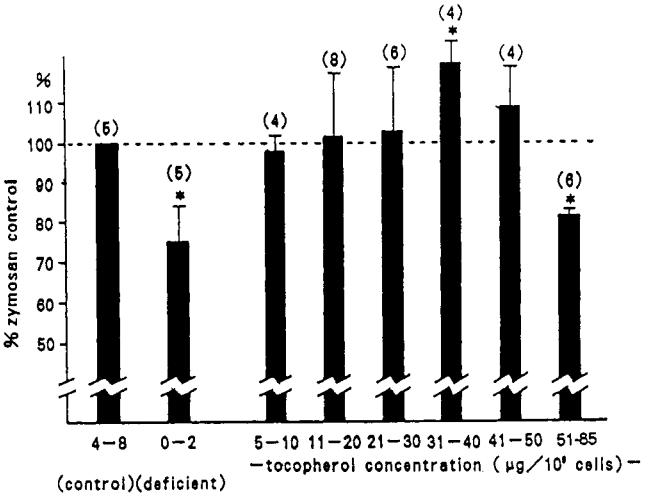

Figure 2. Chemiluminescence in zymosan-stimulated rat PMN as a function of tocopherol concentrations (16). The number of rats examined is shown in parentheses. Mean values ± SD (error bars) are given. Asterisks denote P-value < 0.05 vs the control.

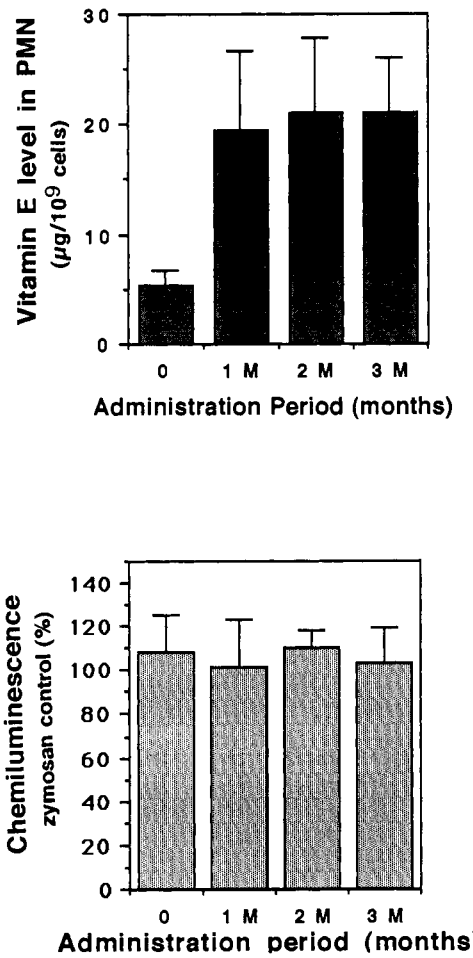

Figure 3. Effect of vitamin E supplementation on zymosan-induced chemiluminescence in human adult PMN (16). Top panel, vitamin E concentrations; bottom panel, chemiluminescence as a percentage of the zymosan control in unsupplemented healthy adults. Mean values (n = 14) ± SD (error bars) are given.

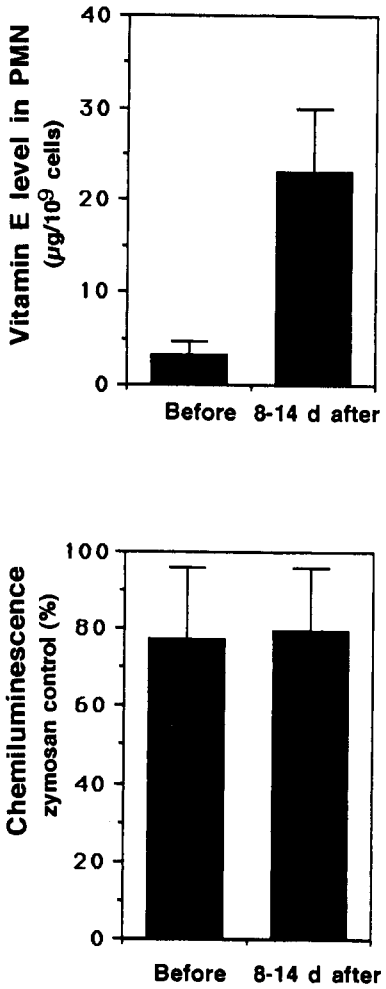

Figure 4. Relationship in newborn PMN between vitamin E and chemiluminescence with zymosan stimulation (16). Top panel, vitamin E concentrations; bottom panel, chemiluminescence as a percentage of the zymosan control in unsupplemented healthy adults. Daily, 40 mg/kg of *all-rac*-tocopherol nicotinate were given to 10 premature newborn infants for 8 to 14 days (n = 8 in "before," 6 in "after").

including necrotizing enterocolitis or sepsis. The serum tocopherol level, which is influenced by serum lipid levels (14, 15), does not usually correlate with the leukocyte tocopherol concentration.

Therefore, we determined the leukocyte tocopherol level and then examined the relationship in leukocytes between tocopherol levels and superoxide anion production (16). The zymosan-induced stimulation of superoxide anion formation in PMN is proportional to the chemiluminescence from added luciferin (2 methyl-6-phenyl-3,7-dihydroimidazol-[1,2-*a*]-pyridin-3-one, a Cypridina luciferin analog). The development of chemiluminescence from PMN has been known to depend on superoxide anion generation, inasmuch as superoxide dismutase completely suppresses it, whereas sodium azide, a peroxidase inhibitor, does not.

The relationship between vitamin E concentrations and superoxide anion production was first examined using rat PMN. Both very low levels of vitamin E and extremely elevated levels suppressed chemiluminescence. The elevated level of vitamin E that suppressed superoxide anion generation was about 10 times higher than the normal level found in rat PMN (Fig. 2).

Thereafter, human leukocytes with elevated tocopherol levels were examined for superoxide anion generation. To obtain leukocytes with elevated tocopherol levels, oral doses of 900 IU (600 mg) of *RRR*-α-tocopherol were administered to 14 young adult male volunteers for 3 months (17). The preparation was a soft capsule, provided by the Eisai Co., Ltd, which was filled with 100 mg of *RRR*-α-tocopherol and cotton seed oil. The subjects were given three equal doses (i.e., each dose = two 100-mg capsules) with meals. The maximal concentration of α-tocopherol in the plasma of these subjects was approximately five times that of unsupplemented adults. The zymosan-induced chemiluminescence in PMN derived from these subjects, however, remained in the normal range (Fig. 3).

Finally, 10 premature infants were treated for 8 to 14 days with oral doses (40 mg/kg/day) of *all-rac*-α-tocopheryl nicotinate, which corresponded to 20 mg of *RRR*-α-tocopherol equivalents. The preparation is a fine powder that can be suspended in milk formula without affecting the gastrointestinal tract due to its low osmolarity. Although vitamin E levels in neonatal leukocytes rose to approximately five times that of adults, the chemiluminescence in neonatal leukocytes with elevated tocopherol levels was not suppressed (Fig. 4). Thus, oral administration of vitamin E may be safe in preterm infants, at least in regard to leukocyte function. However, even though oral administration may be safe, the safety of using preparations with high osmolarity has not yet been proven. Thus, the administration of elevated dosages of oral vitamin E preparations with high osmolarity to premature infants should be avoided. Finally, the dangers of using any parenteral vitamin E preparations are not sufficiently defined. At present, therefore, it is advisable to restrict parenteral use especially in premature infants, not only because of the possible toxicity of detergents in the preparations, but also because unexpectedly elevated concentrations of vitamin E in living cells may have adverse effects on various physiological processes.

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