Tocopherol Excess in Man

CREATINURIA ASSOCIATED WITH PROLONGED INGESTION

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AN ESSENTIAL role for vitamin E in human metabolism has yet to be established. However, its well documented indispensability to certain functions in experimental animals, and its seeming relationship to metabolic abnormalities described in patients apparently depleted of this substance suggest that vitamin E is probably also required by man.

Although tocopherol therapy generally fails to benefit patients with muscular dystrophy, the creatinuria that accompanies the reversible muscular disorders characteristic of vitamin E deficiency in other species may have a clinical counterpart. In a recently reported case of fatal biliary cirrhosis,[1] creatinuria and pentosuria were associated with an absence of measurable tocopherols in the blood serum, and were temporarily alleviated by tocopherol administration. Similarly, vitamin E therapy has inhibited creatinuria in infants with cystic fibrosis of the pancreas and biliary atresia.[2]

The present report describes an instance in which the experimental ingestion of an excess of tocopherol over a period of three months by an apparently normal subject was associated with a transitory creatinuria in the absence of other significant adverse clinical or laboratory effects.

CASE REPORT

A 41-year old physician ingested a total of 296 g of alpha tocopherol over a period of 93 days, in the following dosage: 2 g daily for 37 days; 4 g daily for 55 days; and 2 g on the final day. Two preparations were employed: Ephynal Acetate®† for the first 80 days; and Aquasol E®‡ for the last 13 days. Usually the vitamin was taken in two daily doses about eight hours apart, but there was no rigid adherence to this routine or to any fixed dietary regimen. There was no appreciable change in physical activity during the test period, nor were any significant intercurrent infections incurred.

RESULTS

The principal laboratory findings are indicated in the accompanying table and figure.

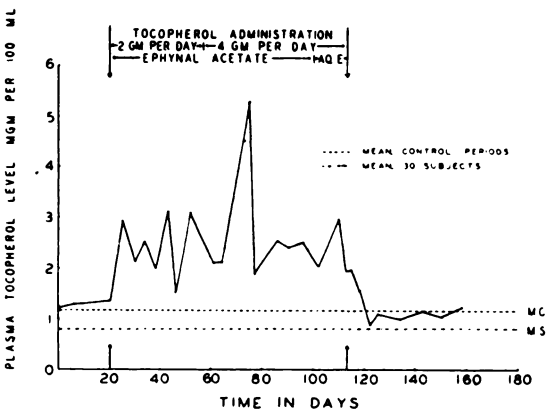

Fig. 1. Blood plasma tocopherol response to ingested vitamin E: 296 g DL-alpha tocopheryl acetate in 93 days.

The plasma tocopherol concentration, measured by a macro adaptation of the method of Quaife *et al.*,[3] showed a rapid initial rise followed by a variable plateau without overall increment, which was maintained throughout most of the test period at approximately twice

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† Ephynal Acetate, Roche, supplied in part through the courtesy of Dr. S. Evert Svenson, Hoffman-La Roche, Inc., Nutley, N. J.

‡ Aquasol E, U. S. Vitamin Corporation.

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TABLE I

Plasma Tocopherol Concentration and 24-hour Urinary Excretion of Creatine and Creatinine Before, During, and Following Excess Tocopherol Ingestion

Observation day	Test period day	Plasma tocopherols*	Urine creatine†	Urine creatinine†
1	−19	1.26		
7	−13	1.39		
19	−1	—	0	1,704
20	1	1.41		
25	6	2.91		
29	10	2.25		
32	13	2.53		
36	17	2.01		
40	21	3.13		
43	24	1.53		
47	28	3.09		
60	41	2.18		
64	45	2.19		
68	49	5.39		
71	52	1.79		
83	64	2.51		
88	69	2.39		
92	73	2.41		
103	84	2.98	151.5	1,313
109	90	1.91		
110	91	—	143	1,324
111	92	1.94		
113	+1	1.53		
117	+5	0.81		
120	+8	1.10		
124	+12	—	0	1,322
130	+18	1.03		
139	+27	1.18	0	1,379
155	+43	1.03		
162	+50	1.24		
169	+57	0.76		
186	+74	1.29		
195	+83	1.29		
228	+116	1.40		

* Mg per 100 ml.
† Mg per 24 hours.

the usual concentration.* It returned rapidly to the pretest range when the tocopherol was discontinued. The mean fasting concentration of 2.26 ± 0.84 mg per 100 ml differed significantly (P less than 0.001) from the mean level of 1.15 ± 0.36 per 100 ml before and after the test period.† The fasting concentration was not appreciably higher on the daily dose of 4 than of 2 g, nor did the substitution of the aqueous dispersion for the nonwater-miscible preparation have any apparent added effect. Tocopherol could not be detected in the urine at times of maximum plasma concentration or over spans of several hours following ingestion of this substance.

A significant creatinuria was noted during the test period. On the day before initiation of the vitamin regimen, creatine was absent from a 24-hour specimen. On the 84th and 91st days of the experiment, the 24-hour excretion totals were 151.5 and 143 mg respectively. Twelve, and again, 27 days after the tocopherol was withheld, creatine could not be detected in 24-hour samples.

Creatinine excretion was questionably altered by the tocopherol ingestion. The output in the 24-hour period before the start of the test was greater by approximately 20 to 25 per cent than quantities measured on two occasions during, and two following, the experimental period. Except for a slight increase 27 days after the preparation was discontinued, these four readings were virtually identical. The excretion of 17-ketosteroids seemed unaffected by the tocopherol administration being 11.3 mg per 24 hours on the day before, and 11.9 mg on the 84th day of the tocopherol regimen. Blood cholesterol, carotene and vitamin A levels, the serum bilirubin level, cephalin flocculation, thymol turbidity, and the prothombin, bleeding and coagulation times showed no significant changes during the test period. The Harvard two-step test for physical fitness, Master two-step test, electrocardiogram and ballistocardiogram were likewise unaffected. Biopsy of the deltoid muscle at the end of the

* Repeated absorption tests showed considerable variation, with no consistent plasma response pattern. In general, following ingestion of amounts up to 4 g in a single dose, plasma tocopherol levels showed only small, gradual changes. Apart from the single fasting level of 5.39 mg per 100 ml, a concentration in excess of 4.0 mg per 100 ml was noted in only one instance, six hours after the ingestion of 4 g of tocopherol.

† The mean plasma level of 1.16 ± 0.39 mg per 100 ml before that period did not differ significantly from the level of 1.12 ± 0.20 mg per 100 ml following the experiment. However, the mean fasting level for this subject (62 readings before and after the test period) of 1.15 ± 0.37 mg differed significantly (P less than 0.0001) from the mean fasting level of 30 other subjects (72 readings) of 0.81 ± 0.26 mg.

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experimental period revealed no deviation from the normal.

Clinically, no abnormalities were noted that could be attributed unequivocally to the large doses of tocopherol consumed. However, chapping cheilosis and angular stomatitis appeared early and persisted variably, but without progression, throughout the ingestion period. Gastrointestinal disturbances were frequent, especially during the final month, when abdominal distress and diarrhea with tenesmus were pronounced. Vague generalized muscle weakness and increased fatigability were experienced toward the end of the test period, but these wholly subjective complaints could not easily be evaluated. The untoward clinical manifestations disappeared within two weeks after the tocopherol was discontinued.

DISCUSSION

The average plasma concentration maintained in this case exceeded the usually accepted range of normal, but was lower than maximum levels reported with much smaller doses.[4–7] Higher levels have also been noted in the last trimester of pregnancy,[8,9] and in certain pathologic states without apparent excess ingestion of this substance.[9–11] The type of preparations employed may have been a limiting factor, and large amounts may have been lost in the stool.[5,12–14] Nevertheless, the lack of progressive increment in the blood, and, as in most other reported instances,[12,15,16] the absence of vitamin E from the urine, suggest that mechanisms other than those of absorption and elimination are involved in regulating plasma tocopherol concentration. Blood levels are temporarily depressed in a number of conditions not affecting intestinal fat transfer,[7,10,17,18] and so-called ceiling effects have also been noted by other observers.[2,18]

Creatinuria, as a phenomenon of tocopherol excess, is unexpected and not readily explained. Vitamin E reportedly influences pituitary-adrenal function and questionably affects the production of 17-ketosteroids.[19–22] Yet the unchanged steroid excretion in the present instance, although based on limited data, suggests that altered creatine metabolism does not result from modified adrenal or testicular activity.*

Tocopherol toxicity is readily produced in experimental animals. Although usually stated not to occur in man,[23] untoward symptoms have been reported on doses of 300 to 1,500 mg per day.[6,24–26] While a different dosage and/or different subject might have yielded higher plasma levels, with or without clinical toxicity, the absence of definite adverse changes in this case suggests an appreciable tolerance for tocopherol. Creatinuria, conceivably, may represent an early, subtle index of induced metabolic malfunction.

SUMMARY

Ingestion of 296 g of alpha tocopherol by a normal adult male over a period of 93 days resulted in a sustained average plasma tocopherol concentration of 2.26 ± 0.86 mg per 100 ml. This was statistically significant and approximately twice the control level of 1.15 ± 0.37 mg per 100 ml. A significant transitory creatinuria occurred during the test period, but there was no apparent change in the excretion of creatinine or of 17-ketosteroids.

There were no unequivocal signs of clinical toxicity. Exercise tolerance seemed unaffected. The electrocardiogram, ballistocardiogram, serum cholesterol, liver function and blood coagulation studies, and a muscle biopsy showed no deviation from the normal.

Creatinuria may be an early manifestation of an adverse metabolic effect induced by vitamin E excess.

ACKNOWLEDGMENTS

Appreciation is expressed to Dr. Philip Cabaud for the creatine, creatinine, cholesterol, liver function and blood coagulation studies; to Dr. David Kydd for the 17-ketosteroid determinations; to Drs. William Noble and Helen Paulino for the Master two-step, electrocardiogram and ballistocardiogram; to Dr. Joseph Whelan for performing, and to Dr. J. Arnold De Veer for interpreting the muscle biopsy; and to Miss Marie Leogrande, who performed all of the vitamin determinations.

* This relationship is being investigated further. Preliminary observations suggest that a transitory creatinuria may, in some instances, be induced by a single large dose (4 g) of tocopherol, without prolonged ingestion of excessive amounts.

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