Role of vitamin E in the aetiology of phrynoderma (follicular hyperkeratosis) and its interrelationship with B-complex vitamins

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1. A study was undertaken to investigate the role of vitamin E in the aetiology of phrynoderma (follicular hyperkeratosis). Fifty-six children with the disease and twenty-one normal children were investigated for this purpose.

2. Plasma vitamin E levels (mean ± se; mg/l) were found to be low in phrynoderma (3.7 ± 0.19) in contrast with normal children (6.6 ± 0.40) and therapy with a combination of vitamin E and B-complex brought about complete cure.

3. The increase in plasma vitamin E levels after the administration of vitamin E at a dose of 100 mg three times daily for 4 weeks was higher than that obtained when vitamin E at the same dose was administered together with vitamin B-complex for 4 weeks, suggesting an interaction between the two vitamins. Further studies are necessary to find out the exact nature of this interrelationship.

Phrynoderma or follicular hyperkeratosis has long been recognized as a nutritional deficiency disorder. It is characterized by the appearance of cone-shaped, horny, hyperkeratinized, scaly eruptions over the dorsal aspects of both limbs. The aetiopathogenesis of this disorder has so far been controversial. Based on the results of studies conducted in India (Gopalan, 1947; Bagchi et al. 1959; Srikantia & Belavady, 1961; Srikantia & Par-gaonkar, 1964; Bhat & Belavady, 1967) it has been suggested that this condition arises from a dietary deficiency of both essential fatty acids (EFA) and B-complex vitamins. In all the studies mentioned previously a vegetable oil rich in EFA (safflower) with or without vitamin B-complex supplements was used for the successful treatment of the disease.

Vegetable oils which are rich sources of EFA are also rich sources of vitamin E. There have however, been no studies done to determine which of these two components in the vegetable oil, namely EFA and vitamin E, is actually responsible for the therapeutic effect obtained with the use of these vegetable oils. A study was therefore carried out to investigate the possible role of vitamin E in the aetiology of phrynoderma.

SUBJECTS AND METHODS

A total of fifty-six subjects suffering from phrynoderma, of whom thirty-seven were males and nineteen were females, were investigated. Their ages ranged from 5 to 15 years. All children belonged to a low socio-economic group. Twenty-one normal children of similar age and socio-economic status were also investigated as controls. All subjects were treated as outpatients, to avoid major alterations in their dietary pattern during the study period.

Fasting blood samples were drawn for estimation of plasma vitamin E and the subjects were allocated serially to one of the following treatment groups: group 1, placebo in the form of glucose dispensed in gelatin capsules; group 2, vitamin E in the form of DL-α-tocopheryl acetate, 100 mg three times daily; group 3, vitamin E 100 mg three times daily together with vitamin B-complex, one tablet three times daily; group 4, vitamin B-complex one tablet three times daily.

The composition of the B-complex tablets used was as follows: thiamine 3 mg, nico-
Table I. Clinical response to various treatment regimens in subjects with phrynoderma

(Values in parentheses are the percentage of the total showing the response)

<table>
<thead>
<tr>
<th>Group no.</th>
<th>Treatment</th>
<th>No. of subjects</th>
<th>Complete improvement</th>
<th>Partial improvement</th>
<th>No improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Placebo (glucose)</td>
<td>13</td>
<td>—</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>Vitamin E†</td>
<td>22</td>
<td>8</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Vitamin E and B-complex</td>
<td>13</td>
<td>10</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>Vitamin B-complex ‡</td>
<td>8</td>
<td>1</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

Statistical comparison of 'complete response' with 'partial and no improvement' by a series of $2 \times 2$ chi-squares (with Yates' correction) gives: placebo (gr. 1) worse than E (gr. 2) (chi-square = 4.24; $P < 0.05$), and E+B (gr. 3) (chi-square = 13.16; $P < 0.001$). E+B (gr. 3) is better than E (gr. 2) (chi-square = 3.88; $P < 0.05$), and B (gr. 4) (chi-square = 5.86; $P < 0.05$). The E (gr. 2) versus B (gr. 4) difference is non-significant (chi-square = 0.66).

† Vitamin E in the form of DL-a-tocopheryl acetate at a dose of 100 mg three times daily.

‡ Vitamin B-complex at a dose of one tablet three times daily; each tablet contained: thiamine 3 mg, nicotinamide 30 mg, riboflavin 1 mg, calcium pantothenate 1 mg, pyridoxine hydrochloride 0.5 mg, cyanocobalamin 5 µg.

Clinical assessment of the subjects. Weekly clinical assessment was done on a double-blind basis. The physician who did the clinical assessment was not aware of the treatment group to which the patient belonged. Therapeutic effect was assessed as: (1), complete disappearance of lesions; (2), partial improvement; (3), no change.

Plasma vitamin E was estimated by the method described by Kayden et al. (1973).

RESULTS AND DISCUSSION

The mean ($\pm$ se) plasma vitamin E level (mg/l) in the fifty-six subjects with phrynoderma was $3.7 \pm 0.19$ which was significantly different ($P < 0.001$) from the corresponding value of $6.6 \pm 0.40$ for the twenty-one normal children. A level of plasma vitamin E below 5 mg/l is generally considered to be indicative of a deficiency of vitamin E (Bieri & Farrel, 1976). In the present study forty-seven of the fifty-six subjects studied had plasma vitamin E levels below 5 mg/l.

The results of the clinical response to various treatment regimens are given in Table I. Vitamin E alone when administered at a dose of 100 mg three times daily (group 2) for 4 weeks produced complete improvement in eight (36%) and partial improvement in thirteen (59%) of the twenty-two subjects. There was a marked contrast in the response of the group given the placebo (group 1) where only two (15%) of the thirteen subjects showed partial response while the remaining eleven (85%) showed no response. Ten (77%) of the thirteen subjects who received vitamins E and B-complex (group 3) showed complete improvement and all the remaining subjects showed some improvement. Administration of vitamin B-complex alone (group 4) for a period of 4 weeks produced partial response in six (75%) of the eight subjects.

Eight of the thirteen group 2 subjects who had shown partial improvement with vitamin E...
Table 2. Effect of different treatment regimens on levels of plasma vitamin E (mg/l) at the end of 4 weeks
(Mean values with their standard errors)

<table>
<thead>
<tr>
<th>Group no.</th>
<th>Treatment</th>
<th>No. of subjects</th>
<th>Initial Mean ± SE</th>
<th>Final Mean ± SE</th>
<th>Difference Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Placebo</td>
<td>13</td>
<td>3.5 ± 0.31</td>
<td>3.4 ± 0.28</td>
<td>NS</td>
</tr>
<tr>
<td>2</td>
<td>Vitamin E</td>
<td>22</td>
<td>3.6 ± 0.32</td>
<td>10.9 ± 0.79*</td>
<td>7.3 ± 0.79</td>
</tr>
<tr>
<td>3</td>
<td>Vitamin E and B-complex</td>
<td>12</td>
<td>4.0 ± 0.37</td>
<td>8.7 ± 0.53*</td>
<td>4.7 ± 0.40†</td>
</tr>
<tr>
<td>4</td>
<td>Vitamin B-complex</td>
<td>7</td>
<td>4.9 ± 0.55</td>
<td>4.5 ± 0.49**</td>
<td>0.4 ± 0.09</td>
</tr>
</tbody>
</table>

NS, not significant.

Final values differed significantly from the initial values (Paired t test); * P < 0.001, ** P < 0.02.
† Value for group 3 differed significantly from that for group 2. (Student's t test) (P < 0.05.)

were then given vitamin B-complex for a further 4 weeks. All subjects showed complete recovery.

The effect of various therapeutic regimens on plasma vitamin E level at the end of 4 weeks of treatment are given in Table 2. There was a significant increase (P < 0.001) in the plasma vitamin E level (mean ± SE; mg/l) from 3.6 ± 0.32 to 10.9 ± 0.79 after the administration of vitamin E, while in the placebo group there was no change. In subjects who received vitamins E and B-complex, the mean (± SE) level (mg/l) increased from 4.0 ± 0.37 to 8.7 ± 0.53. The extent of the increase in this group was however significantly lower (P < 0.05) than that seen in subjects who received vitamin E alone, although both groups received identical amounts of vitamin E. Subjects who had received the vitamin B-complex alone showed a small but statistically significant (P < 0.02) reduction in plasma vitamin E at the end of 4 weeks.

The distribution between the different treatment groups of cases with differing clinical severities, as judged by criteria used in earlier studies (Menon et al. 1950), was found to be similar. Since there was no major change in the pattern of dietary intakes of these subjects during the period of observation, the beneficial effect obtained in different treatment groups can be attributed to the particular intervention introduced. Vitamin E alone was not able to cure phrynoderma completely in a majority of the cases. However, it must be considered significant that administration of vitamin E alone brought about complete improvement in eight of the twenty-two cases and partial cure in thirteen of the cases. In subjects who showed partial cure, after an initial improvement when the lesions became flat, there was no further improvement. Addition of vitamin B-complex at this stage brought about complete cure. A similar observation had been made previously with safflower oil, a vegetable oil rich in EFA. The vegetable oil, when given alone, brought about partial improvement in some cases and the addition of B-complex vitamins brought about complete improvement (Srikantia & Belavady, 1961). In view of the present observation that administration of vitamin E together with vitamin B-complex resulted in a good clinical response, one may perhaps suggest that even in the instance of safflower oil, vitamin E might have been the active principle.

In a considerable proportion of families belonging to low socio-economic groups in India, the amount of fat used in cooking is either negligible or extremely low (Achaya, 1978a). However the predominantly cereal based diets still supply approximately 10 g fat/d (Achaya, 1978b), the linoleic acid contributing between 2 and 4.5% of the total...
energy intake (Achaya, 1978c). The human requirement for EFA is believed to be at least 3% of the total energy intake (FAO, 1977). Thus it appears that the EFA requirements may be met even with the habitual Indian diets. It is however unlikely that the vitamin E requirements are fully met. Vitamin E in cereals, which are the staple in most Indian diets, is predominantly in the form of γ-tocopherol, which is used less efficiently than α-tocopherol (Scott, 1978). It is, therefore, probable that on such diets the vitamin E requirements may not be fully met. However, the exact vitamin E content of Indian diets was not estimated.

The previously mentioned considerations, together with the observation of a positive therapeutic benefit with the administration of vitamin E in combination with vitamin B-complex, lend strong support to the possibility that it was the vitamin E content of the safflower oil which was responsible for the beneficial effect obtained in earlier studies.

The differential increase in plasma vitamin E (after treatment) when vitamin E was given alone or together with B-complex vitamins was unexpected and suggests an interaction between these two vitamins. Interactions between vitamin E and members of the B-complex group of vitamins have been reported earlier (Young et al. 1955; Day & Dinning, 1956; Green, 1962). Most of these observations, however, have been made in experimental animals after inducing deficiency states of either vitamin E or vitamin B-complex. Results presented here indicate that such an interaction may occur even in the human situation. Further studies are in progress to determine the possible interactions of vitamin E with individual members of the vitamin B-complex group and the mechanism of their interaction.

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