Hypervitaminosis A

EXPERIMENTAL INDUCTION IN THE HUMAN SUBJECT

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VITAMIN A toxicity is a well-documented phenomenon. Experimentally, pathological changes are readily reproduced in animals fed an excess of this nutrient[1–6]. Clinically, a characteristic syndrome of chronic poisoning is emerging from reports of patients consuming concentrated preparations of vitamin A over long periods of time.[7–16] Children, particularly, have been afflicted, but at least five instances have been recorded in adults. Gerber, Raab, and Sobel[17] published the most comprehensive of these descriptions and reviewed the literature on the subject. The biochemistry and pathology of hypervitaminosis A have recently been discussed by Nieman and Klein Obbink.[18]

The present report describes the experimental production of hypervitaminosis A in man. The attempt was made to demonstrate relationships between the quantity of vitamin ingested, its concentration in the blood plasma, and clinical and laboratory evidence of a "toxic" reaction to this substance. Repetition of the procedure in the same subject tested the reproducibility of the results and provided some indication of intra-individual variation in response to comparable dosage during two separate periods of administration (Table I).

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METHOD

The subject was a 40-year-old white male physician of moderately athletic habitus, 71 inches in height and weighing 165 pounds. He was in generally good health, although there was a past history of malaria, hepatitis, and dysentery. Prior to, and between—but not during—the two experimental periods five months apart, there was irregular consumption of a multivitamin preparation containing 5000 International Units of vitamin A. In the four-month period ending one month prior to the beginning of the first experimental period, there was additional consumption (by mouth, chiefly, and intravenously) of approximately 2.5 million International Units during a series of vitamin A tolerance tests. Over a period of more than one-half year fasting blood levels had been fairly constant, falling within the range of accepted normal values. No attempt was made to standardize or in any way modify living habits or dietary intake during these tests.

The vitamin A preparation employed was an aqueous emulsion (Aquasol), which has been shown to be better absorbed than the oil preparations incriminated in most reported instances of hypervitaminosis. Although the toxic dose of vitamin A has been variously estimated,[18] it would be expected to prove relatively smaller with this water-miscible product.[19–21]

In the first experimental period, during the month of December, one million units of vitamin A were ingested daily for 13 days, in inconstant portions and at irregular hours between 8:00 a.m. and 10 p.m. Two million units were

ingested within one-half hour on the fourteenth and final day.

Vitamin A adsorption tests were performed on the ninth, eleventh and fourteenth day. In each of these tests, the blood vitamin A level was measured in the postabsorptive state and at intervals of one and four hours after the test dose. One million units were administered in the first two tests, and two million units in the third. The subject fasted throughout the first and last tests, but consumed a small breakfast at the one-hour point in the second—to evaluate the possible effect of eating on absorption of this type of vitamin A preparation.[22]

The second experimental period was in the following May, a time selected to present possible contrasting seasonal influences and to permit a long interval of apparent clinical normality. One million units of the same preparation were ingested daily for a period of 25 days. The effects of ethanol on the plasma vitamin A level were measured in the postabsorptive state on the fifth and thirteenth days of this period. In the first of these, 60 ml of 100 per cent ethyl alcohol (diluted with 200 ml of carbonated water) were taken by mouth, and, in the second, one liter of a 5 per cent solution was administered intravenously over a period of 20 minutes. Blood plasma vitamin A levels were measured before, and at intervals of 1, 2, and 4 hours after the start of each test.

With the exceptions noted in the absorption and ethanol tests, all blood specimens were drawn in the fasting state during control, interval and experimental periods. The plasma vitamin A preparation was measured in duplicate by the ultraviolet irradiation method of Bessey *et al.*,[23] adapted to 3-ml samples.

In the second experimental period the following additional tests were performed: sedimentation rate, serum bilirubin, cholesterol concentration, cephalin flocculation and thymol turbidity, the last four to evaluate possible adverse effects on the liver—the principal storage site of vitamin A. On the final day of this period, roentgenograms were made of the pelvis and of the long bones of the extremities, which are among the principal sites of abnormalities reported in cases of hypervitaminosis A.[5,10,12,17,18]

Dark-adaptation studies were performed on three separate occasions, one before and two during the second experimental period—on the hypothesis that, since some lesions associated with vitamin A excess resemble those resulting from a deficiency of this substance[14] and of other nutrients,[18] a similar effect might be manifested in retinal function.[24–26]

RESULTS

Results are indicated in the accompanying tables and figure.

The responses during the two experimental periods differed considerably—both qualitatively and quantitatively. This was especially true with respect to the clinical manifestations of vitamin A toxicity. In the first period the degree of debility was sufficient to cause vitamin A consumption to be discontinued at the end of two weeks. In the second, the symptoms were most pronounced from the third to the tenth day, following which discomfort and functional inefficiency declined, to remain fairly constant for the remainder of the experiment. However, the subjective "recovery period" was longer following the second test period, about four, compared with two, weeks.

The principal clinical features included the following: headache (severe, often intractable, chiefly frontal and retro-orbital): pruritic dermatitis, including folliculosis and xerosis, notably of the extremities, generalized desquamation, exacerbation of pre-existing seborrhea (principally of the scalp), and an apparent increment in a long-developing alopecia; increased fragility of the fingernails;* cheilosis, with marked chapping and splitting of the lips; epistaxis, slight but persistently induced by blowing the nose; gastrointestinal disturbances, including anorexia, nausea, and alternating constipation and diarrhea with severe

* The increased fragility was noted some three months after each test period, at a time when the segments of nails formed under these abnormal conditions reached the distal margins. There was no significant difference in the measured rate of nail growth between the experimental and control periods.

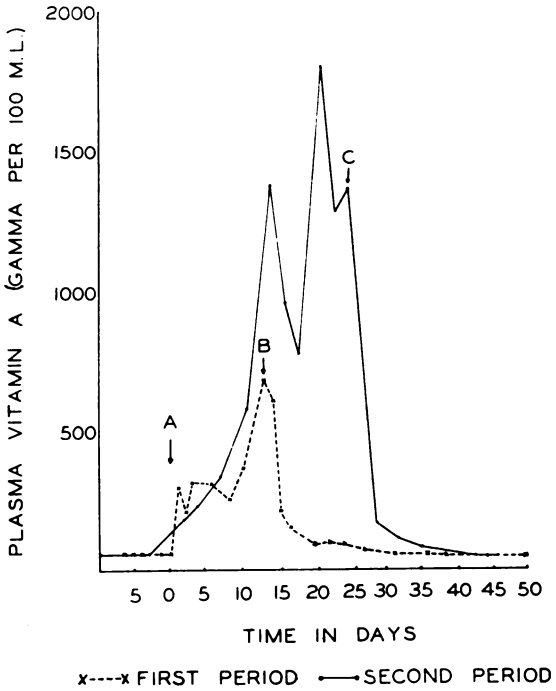

Fig. 1. Blood plasma vitamin A levels during two test periods of ingestion (one million units daily*). *A*, Vitamin A started, both test periods. *B*, Vitamin A discontinued, first test period. *C*, Vitamin A discontinued, second test period.

* Two million units on final day, first period only.

TABLE I

Blood Plasma Vitamin A Concentrations Associated with Ingestion of Excessive Doses

First Period			Second Period		
Date	*Test day	†Vit. A	Date	Test day	Vit. A
12/2	−5	50	4/8	−26	54
12/3	−4	54	4/22	−12	45
12/6	−1	57	4/29	−5	48
12/7	1	62	5/4	3	174
12/8	2	288	5/6	5	232
12/9	3	192	5/9	8	321
12/10	4	298	5/13	12	574
12/13	7	286	5/16	15	1391
12/15	9	247	5/18	17	961
12/17	11	359	5/20	19	784
12/20	14	686	5/23	22	1803
12/21	+1	612	5/25	24	1286
12/22	+2	206	5/27	+1	1368
12/23	+3	144	5/31	+5	156
12/26	+6	98	6/3	+8	125
12/27	+7	79	6/6	+11	84
12/29	+9	85	6/13	+18	64
12/31	+11	78	6/15	+20	60
1/3	+14	67	6/17	+22	61
1/7	+18	52	6/22	+27	66
1/12	+23	58	7/6	+41	45
1/14	+25	53	7/12	+49	59

Mean plasma vitamin A concentration

(a) Before first test period (40 readings from 5/18–11/30/54) 59.5 ± 7.8 with a range of 44–75 μg per 100 ml.

(b) Between test periods (9 readings from 1/24–4/1/55) 47.1 ±6.6 with a range of 42–56 μg per 100 ml.

(c) Following second test period (8 readings from 7/15–9/8/55) 48.4 ± 6.7 with a range of 34–46 μg per 100 ml.

* Days before, during, and following ingestion period.

† Vitamin A concentration in micrograms per 100 ml of plasma.

tenesmus; visual disturbances, including seeming diminished acuity and development of spots before the eyes (one of which has persisted during the seven months since the end of the second test period); transient dizziness; generalized muscle weakness and fatigability; polyarthralgia; and pain and tenderness over the long bones, notably the distal tibia.

These manifestations did not all appear during each experimental period, nor did they necessarily become more severe or remain constant once they became evident. The epistaxis was noted only in the first, shorter period, during which, too, the dermatitis was much more severe and widespread. A generalized desquamation, lasting approximately two weeks, began only after the first course of vitamin A was discontinued. During the second, a much less pronounced desquamation began on the fourteenth day (comparable to the first-period fortnight), continued throughout the remaining days of vitamin ingestion, and persisted for three weeks after it was discontinued.

Most striking and variable among the clinical manifestations were the headache and cheilosis. The former was severe throughout the first period and even more severe during the first week of the second trial, but became mild and inconstant thereafter.

The cheilosis, present continuously after the first few days of both periods, became in-

TABLE II

Blood Plasma Vitamin A Levels During Vitamin A Absorption Tests and in Response to Oral and Intravenous Ethyl Alcohol

Test no.	Date	Test period	Test period day	Test substance and experimental conditions	Plasma vit. A level*			
						Time in hours†		
					Fasting	1	2	4
1	12/15	1	9	Aqueous vitamin A, 1 million units, fasting throughout	247			1001
2	12/17	1	11	Aqueous vitamin A, 1 million units, small meal 1 hour after test dose	359	367		1224
3	12/20	1	14	Aqueous vitamin A, 2 million units, fasting throughout	686	716		3094
4	5/6	2	5	Ethanol, 100%, 60 ml and 200 ml water by mouth, fasting throughout	232	232	268	240
5	5/13	2	12	Ethanol 5%, 1 liter intravenously, fasting throughout†	574	410	424	538

* Vitamin A level in micrograms per 100 ml.

† Time after ingestion of test substance, and from beginning of alcohol infusion (infusion time 20 minutes).

creasingly severe throughout the second period, to disappear finally about two weeks later.

The blood vitamin A patterns were comparable during the two test periods (Fig. 1). Although the first pattern was smoother, both showed an irregular, but generally progressive, rise in plasma concentration, followed by a rapid fall when the vitamin was withheld. However, the relative plateau level of 200 to 300 micrograms per 100 ml during approximately the first half of the first period had no real counterpart in the later trial, and, beyond the initial drop, the falling plasma level also seemed more gradual in the earlier test. Vitamin A was not detected in the urine when the plasma concentration was elevated.

The patterns of the vitamin A absorption tests and the plasma level responses to ethanol are indicated in Table II. In each of the absorption tests, the blood concentration increased by well over 200 per cent (over 300 per cent in two instances). The response did not seem significantly enhanced by the ingestion of food one hour after the administration of the vitamin.

Ethanol by mouth increased the plasma vitamin A level by approximately 15 per cent, but there was no apparent increase following the ethanol infusion. Correction was not made for the dilution factor (1 liter introduced into the blood stream), although similar infusions have been followed by a rise in plasma vitamin A concentration from normal levels in the same subject.

In general, although there was a good correlation between the amount of vitamin A ingested and the resultant blood levels, a corresponding correlation between the blood levels and the clinical manifestations was not observed. The more prolonged convalescence following the second, longer consumption period was, however, more consistent with expectations.

The serum cholesterol, bilirubin, cephalin flocculation, and thymol turbidity tests showed no significant changes during the experimental period in which these were performed. The blood sedimentation rate fluctuated from normal to slightly elevated readings, but there was no apparent correlation between this rate and the plasma vitamin A level. Dark-adaptation measurements did not vary significantly during the test period, and ophthalmologic examination at the conclusion of the experiment revealed no unusual findings.

DISCUSSION

The manifestations of vitamin A toxicity observed in this experimental production of the syndrome are similar to those reported in cases of accidental poisoning with this substance. The principal features of the present

study are (1) the apparently poor correlation between the blood plasma levels and the clinical reaction to excess vitamin A, and (2) the different responses in the same subject at different times.

The probable influence of factors other than the amount of vitamin consumed must, of course, be considered.[19,27,28,29] Mild, unnoted, intercurrent infections could conceivably have contributed to the symptoms and influenced plasma vitamin A concentrations. Emotional reactions, engendered by concern over toxic manifestations, undoubtedly modified subjective observations, at least. The more pronounced skin reactions noted during the first test period may have resulted in part from the colder weather that commonly conduces to the development of follicular and xerotic lesions in particular.

The generally less severe clinical picture during the second experimental period suggests that observed variations were not related to an excess of vitamin A retained (in the liver) over the interval of five months.[18]

Hypervitaminosis A, representing an abnormal concentration of this substance in the blood plasma, and, presumably, in other tissues, is apparently not synonymous with clinical toxicity referable to an excessive intake of this substance. Comparable to the experience of Arctic explorers, whose acute illness shortly following the ingestion of polar bear liver has been attributed to the large concentrations of vitamin A in this organ, i.e., to acute poisoning,[30] the evidence suggests that symptoms reflect, at least in part, a relative individual hypersusceptibility. As in the case of vitamin D—with which it has much in common—untoward reactions to this fat-soluble vitamin probably occur in only a small number of individuals consuming excessive quantities. Moreover, there seem to be states of relative refractoriness to vitamin A therapy, analogous to vitamin D-resistant rickets. These instances, like relative resistance to clinical toxicity, may possibly be eliminated by the use of better absorbed, aqueous preparations, such as the one used in this experiment.[19–21]

Depending on the criteria used, this case could be regarded as an example of either acute or chronic vitamin A toxicity.[13] Moreover, since many of the symptoms and signs, particularly in the skin, are evidently observed in both types of poisoning, the clinical distinction between acute and chronic syndromes appears artificial and necessarily arbitrary in some instances. Beyond a limited capacity for storage, destruction, or other effective metabolic neutralization (but evidently not excretion) of vitamin A,[18] toxicity caused by this substance would seem to relate to a pharmacologic constant—the product of dose and duration—in which the factor of intensity can be substituted to some degree for that of time, in bringing about a given physical effect. As suggested by the symptom pattern during the second experimental period, the response to absorption tests, and by other reports of clinical toxicity,[16] some adaptation to hypervitaminosis A evidently can occur, with a concomitant modification of the clinical picture. Comparable periodicity of symptoms with temporary spontaneous remissions has been noted in experimental animals.[18] In man, too, apparent compensation for high vitamin intakes, through mechanisms which regulate plasma concentrations, has been described.[27]

The results of the present study confirm the protean manifestations of vitamin A toxicity and the particular predilection for the skin and its derivatives, the hair and nails. More significantly, they establish the existence of intra-individual variation in response to excessive doses of this substance and suggest that the imponderable factor of the human host determines to a very considerable degree the clinical picture (if any) associated with hypervitaminosis A.

SUMMARY

Hypervitaminosis A was induced experimentally in a normal human subject on two separate occasions through ingestion of excessive quantities of this substance during periods of 14 and 25 days, respectively.

The associated clinical picture resembled that of accidental vitamin A poisoning. The skin was most prominently affected. The plasma vitamin A concentration increased

markedly, and appeared to be more closely correlated than the clinical picture with the quantity of vitamin A ingested.

Differences in the responses to comparable doses during the two test periods seemed to reflect principally a considerable intra-individual variation in susceptibility to poisoning with this nutrient.

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