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STUDIES IN ORAL LEUKOPLAKIAS

VII. FURTHER INVESTIGATIONS ON THE EFFECTS OF VITAMIN A ON KERATINIZATION

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In a previous study of 16 patients with oral leukoplakias residing in San Francisco *(Silverman, Renstrup & Pindborg,* 1963), it was shown that vitamin A administered locally in troche form induced temporary partial or complete remissions of some lesions. A continuation series was conducted in Copenhagen in order to further observe and characterize this effect of vitamin A. The purpose of this paper is to report: 1) the clinical, histologic, cytologic and hematologic findings; 2) to compare them with the results of the previous series; and 3) to discuss possible interrelationships between leukoplakias, keratinization and carcinogenesis.

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PRESENT STUDY

Material and Methods

Nineteen patients with oral leukoplakias were evaluated during this investigation. Leukoplakia was defined similarly as in the previous study as any white patches or plaques on the oral mucous membranes that: 1) cannot be removed by scraping, 2) cannot be reversed by removing obvious irritants, and 3) cannot be classified clinically or microscopically as another diagnosable disease. Of the patients, 13 were males and 6 were females. Their ages ranged from 37 to 74 years. Ten of these patients have been followed clinically and histologically from 6 months to 7 years for their lesions. Prior to studying the effect of vitamin A, attempts to induce remissions were made by: 1) reducing or stopping tobacco habits and 2) smoothing teeth or constructing latex splints to preclude or minimize dental trauma to the mucosa.

Vitamin A acetate[1] was given as 75,000 unit troches. The patients were instructed to hold a troche, until it was dissolved, against the lesion to be examined. Since our previous study indicated a response from 2 to 3 weeks after administration of large dosages, 10 troches (750,000 units) per day were prescribed. Observations were made at 1 and 2 week intervals.

Before dispensing the vitamin A troches, the following material was obtained: photographs, cytologic smears, blood for serum vitamin A and carotene determinations, and 5 mm punch biopsies from the lesion and adjacent clinically normal appearing mucosa. The specimens were fixed in cold calciumbuffered formalin, embedded in paraffin, cut and stained with hematoxylin and eosin, van Gieson, a modified Mallory and Papanicolaou stains. Histochemical reactions for oxidative enzymes, proteins, carbohydrates and lipids will be studied and reported in subsequent papers.

Each individual study was terminated when one of the following events took place: 1) complete remission, 2) toxic side effects, 3) patient unwillingness to continue or 4) no indication that continued administration would further alter the lesion.

[1] Vi Dome A tablets, Dome Chemicals Inc., N. Y.

On the last day of administration, photographs, cytologic smears, blood samples and biopsies were obtained. The patients were followed for at least 2 two-week observation periods and then scheduled for longer follow-up periods.

Histologic Classifications

The following terms are used to describe the oral epithelium studied in this investigation:

Keratinization: the biochemical process leading to formation of keratin.

Cornification: the morphologic appearance of cells or cell layers in which keratinization assumingly has taken place.

Hyperorthokeratosis: a pathologic condition in which the superficial layers of the epithelium are cornified, containing no nuclei and appearing homogenous and strongly acidophilic. In areas where orthokeratosis normally occurs, it has to exceed the expected thickness to be called hyperorthokeratosis.

Hyperparakeratosis: a pathologic condition in which the outer cells and cell layers are flattened, contain pyknotic nuclei and exhibit a marked acidophilia. In areas where parakeratosis normally occurs, it has to exceed the expected thickness to be called hyperparakeratosis.

Hyperplasia: a pathologic condition characterized by an enlargement of the prickle cell layer due to an increased number of cells.

Atrophy: a pathologic condition in which the thickness of the prickle cell layer is reduced doe to a decreased number of cells.

Atypia: a pathologic condition featured by a disorderly maturation of the epithelium. The changes comprise one or more of the following: irregular epithelial stratification, increased density of the basal layer or spinal cell layer or both, increased number of mitotic figures, alterations in the nuclear-cytoplasmic ratio, loss of polarity of cells, hyperchromatism and nuclear atypism. Abnormal mitoses are never observed in epithelial atypia and the basement membrane is always intact.

Findings

Table 1 indicates the various responses to vitamin A of the 19 patients. Five male patients had complete remissions, and 5 males and 5 females showed partial remissions. All demonstrated

Table 1.

Effects of Vitamin A on Oral Leukoplakias

Patient	Age	Sex	Site	Vitamin A		Remission
				Daily Dosage (I.U.)	Duration (Days)	
1	43	♂	Commissures	450,000	23	Partial
2	43	♂	Cheeks	750,000	21	Partial
3	70	♂	Cheeks	600,000	21	Complete
4	70	♂	Cheek	750,000	32	None
5	69	♀	Palate	750,000	14	Partial
6	51	♂	Commissures	750,000	16	Complete
7	69	♀	Tongue	600,000	16	None
8	56	♀	Tongue	600,000	14	Partial
9	58	♂	Cheek	750,000	23	None
10	74	♂	Pillar	750,000	18	Complete
11	76	♂	Cheek	750,000	13	Complete
12	55	♀	Cheek	600,000	16	Partial
13	48	♂	Cheek	750,000	14	Partial
14	52	♂	Commissures	750,000	23	Partial
15	72	♀	Tongue	600,000	14	Partial
16	47	♂	Commissures	600,000	14	None
17	46	♂	Tongue	750,000	12	Partial
18	37	♀	Commissures	450,000	12	Partial
19	64	♂	Commissures	750,000	12	Complete

recurrences within 2 weeks. The remaining 4 patients did not have any significant improvements of their lesions. Where remissions took place, the maximum changes occurred within a 2-week period.

Table 2 classifies histologically the lesions studied and compares clinical and microscopic changes induced by vitamin A. Leukoplakias, histologically showing either hyperorthokeratosis

Table 2.

Clinical and Microscopic Comparisons of Leukoplakias in Response to Vitamin A

Patient	Sex	Remission	Keratoses		Prickle Cell Layer		Inflammation		Comments
			Before	End	Before	End	Before	End	
3	♂	Complete	Hyperortho Hyperpara	Hyperpara	Normal	Normal	+		
6	♂	Complete	Hyperpara	↓ Hyperpara	Atrophy Hyperplasia	Normal	+	↓ +	Speckled
10	♂	Complete	Hyperortho Hyperpara	Hyperortho None	Atrophy Hyperplasia	Atrophy Hyperplasia	+	+	Speckled Epithelial Atypia
11	♂	Complete	Hyperortho	None	Atrophy	Normal		+	
19	♂	Complete	Hyperpara Hyperortho	Hyperpara	Atrophy Hyperplasia	Atrophy Hyperplasia	+	+	
1	♂	Partial	Hyperpara	↓ Hyperpara	Atrophy Hyperplasia	Atrophy Hyperplasia	+	+	Speckled
2	♂	Partial	Hyperpara None	None	Hyperplasia	Atrophy	+	+	
5	♀	Partial	Hyperpara None	Hyperpara None	Hyperplasia Atrophy	Hyperplasia Atrophy	+	+	Speckled Epithelial Atypia
8	♀	Partial	Hyperortho	Hyperortho	Normal	Normal	+	+	
12	♀	Partial	Hyperortho	Hyperpara None	Atrophy	Atrophy		+	
13	♂	Partial	Hyperortho	Hyperpara	Normal	Normal	+	+	
14	♂	Partial	Hyperortho	Hyperortho Hyperpara	Atrophy	Normal	+		
15	♀	Partial	Hyperortho	Hyperpara	Normal	Normal		+	
17	♂	Partial	Hyperortho	None	Normal	Hyperplasia	+		
18	♀	Partial	Hyperortho Hyperpara	Hyperpara	Normal	Normal	+	+	
4	♂	None	Hyperortho	Hyperortho	Atrophy	Atrophy	+	+	
7	♀	None	Hyperortho	↓ Hyperortho	Atrophy	Atrophy		+	
9	♂	None	Hyperpara	↓ Hyperpara	Hyperplasia	Normal	+	+	
16	♂	None	Hyperpara	↓ Hyperpara	Atrophy Hyperplasia	Atrophy Hyperplasia	+	↓ +	Speckled

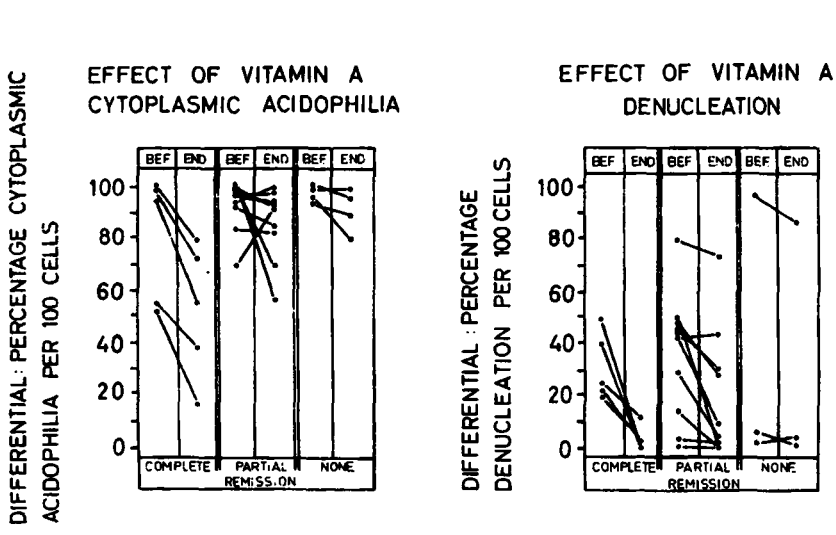

Fig. 1.

or hyperparakeratosis or a combination of both, have the capacity to respond to vitamin A when applied locally. In 16 of the 19 patients, the epithelium transformed microscopically to lesser degrees of cornification or became unkeratinized. In the 3 other patients, 2 of whom showed partial clinical remission of their lesions, there was no evidence of histologic changes. Variations in the width of the prickle cell layer showed neither a consistent response to vitamin A nor to clinical changes. The presence, absence or change in inflammation showed no correlative pattern with alterations of the lesions. Two patients with epithelial atypia clinically improved during vitamin A administration. Specimens from adjacent normal appearing mucosa all microscopically displayed normal morphologic characteristics before and at the end of vitamin A administration.

Effects of vitamin A reflected by exfoliated cells are presented in Figure 1. These data obtained from cytologic scrapings illustrate a tendency towards a decrease of denucleation and cytoplasmic acidophilia.

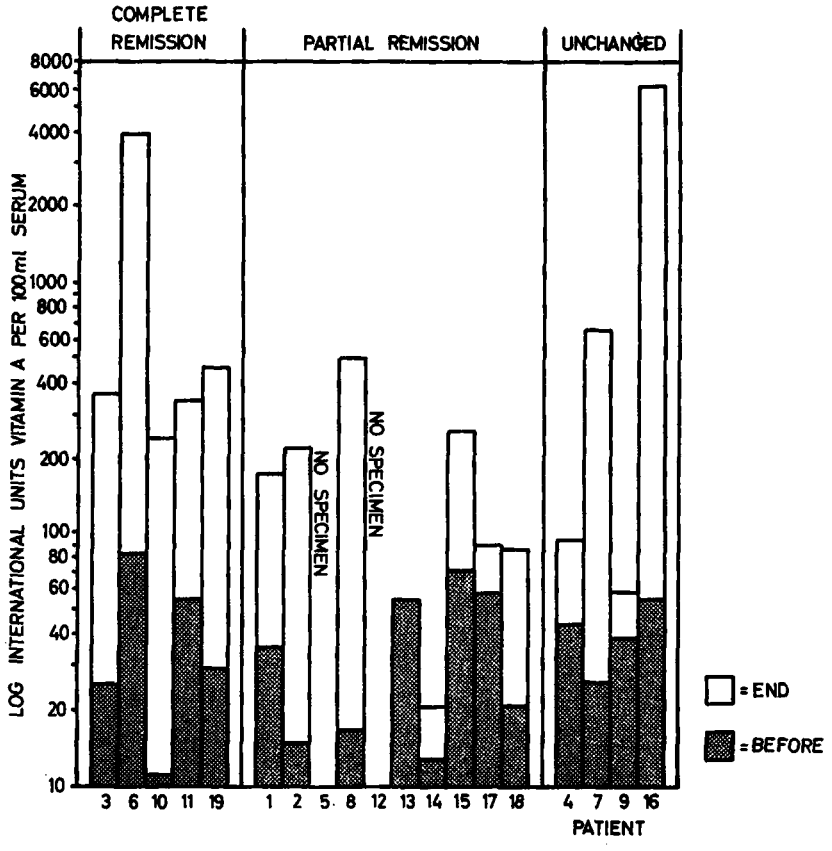

Fig. 2.

Patient serum vitamin A levels before and at the end of vitamin A administration are compared in Figure 2. The increase in serum levels bears no correlation to the responses either of remission or toxicity. Serum carotene levels were unaffected (Table 3).

Eleven of the 19 patients experienced side effects from the vitamin A (Table 4). Combinations of dry skin, pruritus and skin rash were the most common findings. Upon discontinuation of the vitamin, the signs and symptoms would disappear within 2 weeks. No correlation was apparent between the amount of increase of serum vitamin A level and the appearance of side

effects. Three of the eleven patients with toxic manifestations were prematurely discontinued until the signs and symptoms disappeared. Upon readministration of a reduced daily intake (750,000 to 600,000 units), all 3 patients were able to participate in the study free of toxic side effects.

The oral dissolution times for the troches showed no correlation with clinical responses (Figure 3).

Physical examinations and histories revealed no significant associated medical findings. Also, removal of all oral irritants

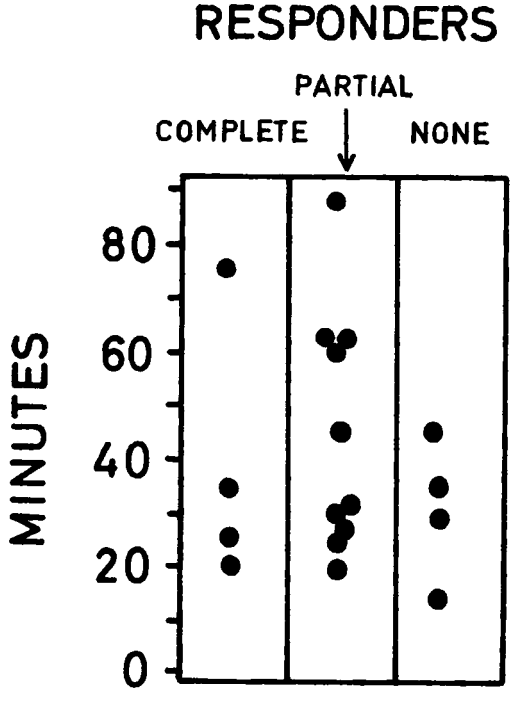

Fig. 3.

Dissolution time for 75,000 units vitamin A troches.

Table 3.

Serum Carotene in Response to Vitamin A

Time of Administration	Patients	No.	Serum Carotene				
			Range μg/100 ml	Average μg/100 ml	Increase	Decrease	Unchanged
Before	All	16	13—77	28	—	—	—
End	Complete Remission	5	16—29	29	0	2	3
	Partial Remission	7	18—87		3	1	3
	Unchanged	4	8—56		2	2	0

Table 4.
Vitamin A Toxicities

Patient	Dosage per Day (I.U.)	Onset of Signs and Symptoms (Days)	Vitamin A Blood Levels in I. U. at End of Administration	Increase over before Administration Levels	Dry Skin	Rash	Pruritus	Swollen Eyes	Dry, Burning Mouth	Angular Cheilitis	Headache	Disappearance of Signs and Symptoms (Weeks)
1	450,000	9	176	×5						+		2
2	750,000	14	226	×15	+	+	+			+		2
3	750,000	12	326	×13	+		+					1
4	750,000	23	97	×2	+	+	+	+			+	2
5	750,000	7	—	—			+		+	+		2
6	750,000	14	3950	×48					+	+		1
7	750,000	8	678	×25		+	+	+				1
8	600,000	10	538	×32	+							1
12	600,000	8	—	—	+		+					2
14	750,000	20	21	×2			+					1
16	750,000	8	6580	×116		+	+					2

did not lead to remission of any lesions. Therefore, all the leukoplakias studied were considered to be of unknown origin.

DISCUSSION

On 2 different patient populations, one of 16 from San Francisco *(Silverman, Renstrup & Pindborg,* 1963), and one of 19 from Copenhagen, similar responses to vitamin A troches used locally on oral leukoplakias were observed. In both series, one quarter of the patients experienced complete remission. All of these 9 patients were males, while the overall sex distribution in both series was 23 males and 12 females. Even though the majority of women patients were post-menopausal, differences in tissue steroid concentrations may still be suspected.

In rats, an antagonism between vitamin A and estrogen has been demonstrated (*Kahn* 1954); and *Fell* (1963) has demonstrated an antagonism between vitamin A and hydrocortisone in an organ culture system using the epidermis of chicken embryos. In attempting an explanation of this phenomenon, *Fell* states that autoradiographic studies in her laboratory with radioactive cystine an inorganic sulphate suggest that basal cells and early differentiated cells in keratinizing epithelium have a mechanism for producing sulphated mucopolysaccharides. This mechanism, which is lost during keratinization, is not stopped in the presence of vitamin A. She speculates that lysosomal proteases are released which break down the precursors of keratin in the epidermal cell (*Dingle* 1961), and that certain steroids may inhibit the release of these hydrolases.

However, this is not an all or none response, for half of the partial remissions occurred in female patients. It is interesting to note that in 2 previous reports (*Zegarelli,* 1959; *Fryer,* 1961), the 3 patients who experienced complete remissions in response to vitamin A were males. The large series of *Smith* (1962) did not differentiate the responders by sex. *Mulay & Urbach* (1959) report that one of the two complete responders to vitamin A was a female.

The fact that remissions to vitamin A occur, prompts two important avenues of investigation. First, it allows an opportunity

for a stepwise study of the keratinization process underlying most leukoplakias. Such data combined with natural histories may yield clues, not only to the basic steps of keratinization, but also to carcinogenesis, which is definitely related to some leukoplakias (*Pindborg, Renstrup, Poulsen & Silverman* 1963). Second, if reversing leukoplakias may prevent the occurrence of some carcinomas that are unpredictably associated with these lesions, a search should be intensified for substances with vitamin A-like activity, that have antagonistic actions on keratinization without vitamin A toxicity.

No attempt was made in this study to utilize or analyze vitamin A as a therapeutic measure. High dosages of vitamin A were used to insure a maximum response in a high percentage of patients. There is no apparent correlation between age, site of lesion, histologic type or serum vitamin A levels and either remissions or toxicities. It is of interest that remissions and recurrences of leukoplakia take place between 1 and 2 weeks. However, in one patient (No. 19) at the end of a 4-week post-vitamin follow-up period, the lesion still appeared markedly improved compared to the initial appearance. This prolonged improvement also occurred in one patient in the previous series.

An increase in the number of mitotic figures was observed in all specimens at the end of vitamin A administration. Increases in mitotic figures suggest that there may exist a relationship between the site of action of vitamin A on nuclei that are still mitotically active, epithelial renewal rates, and time needed during maturation for cornification to take place. This supposition is indirectly supported by the observations of transformations of hyperparakeratosis and hyperorthokeratosis to lesser degrees of cornification, which may be due to stimulation of mitotic activity and acceleration of epithelial turnover. Also, *Renstrup* (1963) reported that the mitotic activity of a group of leukoplakic specimens classified as hyperparakeratotic was 4 times greater than that of a group of lesions classified as hyperorthokeratotic. On the other hand, there is much laboratory data indicating effects of vitamin A on various biochemical systems that may antagonize keratin formation (*Balakhovsky & Drozdova* 1957, *Dingle* 1961, *Fell* 1963, *Flesch* 1962).

Jackson & Fell (1963) have demonstrated electronmicrosco-

pically that vitamin A on embryonic chicken skin in organ culture leads to a lack of density and disappearance of filaments in basal cells. These filaments, when present, coalesce to form tonofibrils, which are associated with keratin formation. They again suggest that vitamin A may inhibit the synthesis of this fibrous protein or catabolyze the fibers after synthesis by releasing cellular hydrolases. At the present time, the differences in cornification of the various oral mucosal sites have been explained only by functional irritation. In studying 4 oral regions of a group of mice, *Meyer, Medak & Weinmann* (1960) have indicated relationship between mitotic indices, growth rates and epithelial width.

Five of the patients demonstrated clinically speckled-appearing leukoplakias, which have been associated with epithelial atypia and carcinoma *(Pindborg, Renstrup, Poulsen & Silverman* 1963). Two of these patients were classified microscopically as epithelial atypia, which is assumed to be a premalignant change. It is interesting that these two patients, as well as an additional patient with a speckled-appearing lesion without associated microscopic epithelial atypia, experienced clinical remissions of their lesions after vitamin A administration. *Smith* (1962) reported on 34 patients with lesions classified as dyskeratotic or premalignant. After 300,000 to 600,000 units of vitamin A for periods varying from 3 to 6 months, he stated that the lesions showed some epithelial improvement without any changes in the microscopic picture.

Specimens were obtained from adjacent normal appearing mucosa, as well as from the lesions, before and at the end of vitamin A administration. This tissue will be studied by histochemical techniques for changes in proteins, carbohydrates and lipids. The material may yield contrasts between normal and abnormal features of keratinization, leading to clues to leukoplakia and carcinogenesis.

Cytologic scrapings revealed abnormal cells from the 2 patients with epithelial atypia. This prompted further investigations and indicates the value of this technique as an adjunct to biopsy. The other 17 patients in this study all exhibited normal exfoliative cytologic smears, except for increased cytoplasmic acidophilia, denucleation and occasional nuclear enlargement. After

vitamin A administration, there was in most instances a reduction of acidophilia and denucleation, but a slight increase in nuclear size. It is not known whether the acidophilia observed in these cells is associated with cell aging, keratin formation or some other biochemical phenomena. Some of the discrepancies in results of the differential counts in the partial responder group may be due to inadequate sampling. It is interesting to observe that although biopsy sections of hyperorthokeratotic specimen give an appearance of the stratum corneum being an amorphous mass of protein, careful cytologic scrapings indicate that most or all of the superficial cells are still intact.

A previous report (*Silverman, Renstrup & Pindborg* 1963) discussed both the historical aspects and potential mechanisms of action of vitamin A, and presented a detailed analysis of the clinical and laboratory findings. The present study has not contradicted any of the assertions made in that article. However, several observations of variances can be made. The serum vitamin A levels in the Copenhagen patients were uniformly lower than those of the San Francisco group. This may be explained either by a difference based upon geographic location and environment or by a difference induced by handling of the specimens, although the same laboratory and analytical procedure were used. In the previous series, a mucous metaplasia was reported in one case after 6 weeks. No such change was seen in the present study. This may have been due to the much shorter vitamin A exposure time utilized in the Copenhagen group.

Further reports derived from material obtained in this study dealing with mitotic activity, electronmicroscopic observations and histochemical evaluations will be forthcoming.

SUMMARY

Nineteen patients with oral leukoplakias were given 450,000 to 750,000 units of vitamin A daily in troche form for periods ranging from 2 to 5 weeks. Five male patients had clinically complete remission of their lesions, while 5 other males and 5 females experienced partial remission. After discontinuing vitamin A, all lesions recurred within 2 weeks.

At the end of vitamin A administration, the microscopic examiations showed that 16 of the 19 lesions had transformed to lesser degrees of cornification or became unkeratinized. In 3 lesions, 2 of which showed partial clinical remission, there were no histologic evidences of epithelial changes.

Serum vitamin A levels increased from 2 to 100 times the pre-vitamin levels. However, the serum concentration showed no correlations with responses. Eleven patients showed side effects from the vitamin A. Dry skin, pruritus and rash were the most frequent toxic signs and symptoms.

Exfoliative cytology reflected the antagonistic effect of vitamin A on keratinization. Comparing before and end-of administration specimens, there were general decreases in cytoplasmic acidophilia and denucleation. From 2 patients, cells suspicious for malignancy were obtained, the histologic sections in both cases were interpreted as epithelial atypia. Both patients showed temporary remission in response to vitamin A.

The results of this study on a group of patients from Copenhagen were similar to those reported previously on a group of patients from San Francisco.

Tissue obtained during this study will be evaluated for mitotic activity, ultrastructure with electronmicroscopy, and histochemical reactions for enzymes, proteins, carbohydrates and lipids.

The mechanism of action, which is assumed to be a local effect, is discussed.

RÉSUMÉ

ÉTUDES SUR LES LEUCOPLASIES BUCCALES

VII. RECHERCHES COMPLÉMENTAIRES SUR LES EFFETS DE LA VITAMINE A SUR LA KÉRATINISATION

Dix-neuf patients présentant des leucoplasies buccales ont reçu, sous forme de tablettes, des doses de 450.000 à 750.000 unités de vitamine A par jour pendant des périodes allant de 2 à 5 semaines. Cinq patients du sexe masculin ont présenté une rémission complète des signes cliniques, tandis que cinq autres

sujets du sexe masculin et cinq sujets du sexe féminin présentaient une rémission partielle. Après arrêt de l'administration de vitamine A, on a assisté à une récidive de toutes les lésions en l'espace de deux semaines.

A la fin de l'administration de vitamine A, l'examen microscopique a révélé que 16 lésions sur 19 avaient évolué vers un moindre degré de kératinisation ou même vers une absence de kératinisation. Dans 3 lésions, dont 2 présentant une rémission clinique complète, l'examen histologique révélait l'absence d'altérations épithéliales.

Le taux de vitamine A dans le sérum augmentait de 2 à 100 fois par rapport au taux avant administration de vitamine A. Le taux du sérum ne présentait cependant pas de corrélation avec la réponse au traitement. Chez onze des patients, il s'est produit des réactions secondaires à la vitamine A. Sécheresse de la peau, prurit et éruptions ont été les signes d'intoxication les plus fréquents.

L'examen cytologique des squames reflétait l'action antagoniste de la vitamine A sur la kératinisation. Si l'on compare des specimens avant administration et des specimens après administration de vitamine A, on observe une diminution générale de l'acidophilie du cytoplasme et de la dénucléation. Chez deux patients, des cellules suspectes de malignité avaient été recueillies. Les coupes histologiques avaient dans les deux cas été interprétées comme des cas d'atypie épithéliale. Ces deux patients ont réagi à la vitamine A par une rémission temporaire.

Les résultats de cette étude faite sur un groupe de patients de Copenhague étaient similaires aux résultats référés précédemment concernant un groupe de patients de San Francisco.

Les tissus recueillis au cours de cette étude seront considérés en ce qui concerne l'activité mitotique, en ce qui concerne l'ultrastructure, à l'aide du microscope électronique, et en ce qui concerne les réactions histochimiques pour déceler les enzymes, les protéines, les hydrates de carbone et les lipides.

Le mécanisme de cette action, probablement un effet local, fait l'objet d'une discussion.

ZUSAMMENFASSUNG

UNTERSUCHUNGEN ÜBER LEUKOPLAKIEN DER MUNDSCHLEIMHAUT

VII. WEITERE UNTERSUCHUNGEN ÜBER DIE WIRKUNG DES VITAMINS A AUF KERATINISIERUNG

Neunzehn Patienten mit Leukoplakien der Mundschleimhaut wurden in Perioden von zwei bis fünf Wochen 450.000 bis 750.000 Vitamin-A-Einheiten in der Form von Pastillen gegeben. Fünf männliche Patienten zeigten eine vollständige klinische Heilung ihrer Affektionen, während fünf andere männliche sowie fünf weibliche Patienten eine teilweise Heilung zeigten. Nach Beendigung der Eingabe von Vitamin A traten alle Affektionen innerhalb von zwei Wochen wieder in Erscheinung.

Gegen Ende der Vitamin-A-Eingabe ergaben mikroskopische Untersuchungen, dass 16 aus den 19 Leukoplakien sich in leichtere Grade der Keratinisierung geändert hatten bzw. ohne Keratinisierung geworden waren. In drei Fällen, wovon 2 eine teilweise klinische Heilung zeigten, wurden keine histologischen Anzeichen epithelialer Änderungen vorgefunden.

Der Vitamin-A-Spiegel im Blutserum stieg auf das zwei- bis hundertfache des Niveaus vor der Behandlung an, aber die Konzentration im Serum zeigte keine Übereinstimmung mit der örtlichen Wirkung. Elf Patienten zeigten Nebenwirkungen aus der Vitamin-A-Behandlung. Trockene Haut, Pruritus und Ausschläge waren die häufigsten toxischen Erscheinungen.

Zytologische Untersuchungen abgestossener Zellen zeigten die antagonistische Wirkung des Vitamins A auf die Keratinisierung. Durch Vergleiche von Zellenproben aus der Zeit vor und der Zeit nach der Behandlung wurde ein grosser Rückgang im Hinblick auf zytoplasmatische Acidophilie und Denukleation festgestellt. Bei zwei Patienten wurden Zellen vorgefunden, die der Bösartigkeit verdächtig waren. Die histologischen Änderungen wurden in beiden Fällen als Epithelatypie gedeutet. Beide Patienten zeigten vorübergehende Besserung nach einer Behandlung mit Vitamin A.

Die Ergebnisse aus dieser Untersuchung einer Gruppe von Patienten aus Kopenhagen stimmten mit den früher veröffentlichten Ergebnissen betreffend eine Gruppe von Patienten aus San Franzisko überein.

Im Verlaufe dieser Untersuchung eingesammelte Gewebeproben werden einer genaueren Untersuchung auf mitotische Aktivität, Ultrastruktur (mittels Elektronenmikroskopie) und histochemische Reaktionen auf Enzyme, Eiweisstoffe, Kohlenhydrate und Fettstoffe unterworfen.

Der Wirkungsmechanismus, der als eine örtliche Wirkung angesehen wird, wird erörtert.

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