TOPICAL VITAMIN-A-ACID IN ACNE

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Vitamin-A-acid or retinoic acid (VAA), a metabolite of vitamin-A (1), was identified chemically more than 30 years ago. When given to vitamin-A deficient rats it corrects the growth defect of vitamin-A-deficiency, stimulates differentiation of epithelial tissue, and alters normal bone growth and metabolism, but does not satisfy the visual and reproductional functions of the vitamin.

In dermatology VAA was first used in ichtyosiform dermatoses and dyskeratoses in 1959 (2, 3). Some years later Christophers and Braun-Falco (4) demonstrated that it stimulated epidermal mitoses and related enzymes. In 1969 Kligman, Fulton & Plewig (5) reported that topical VAA was beneficial in the management of acne. The clinicalvalue was compared with that of benzoyl peroxide, sulphur-resorcinol, and an inert vehicle. The order of increasing therapeutic efficacy was vehicle, sulphur-resorcinol, benzoyl peroxide and VAA. The study could be critisized because it was not conducted in a double-blind manner. However, Kligman (6) doubts that double-blind studies can be performed comparing retinoic acid to a placebo since erythema and peeling easily identifies the active agent. This to a certain extent may be true.

Double-blind studies, however, have been performed (7, 8) and in one of them (7) the placebo, a vanishing cream, showed erythema and peeling in 40% of the patients compared to 81% and 86% in two groups treated with VAA 0.02% and 0.05%. The study which was conducted by J. Christiansen from our hospital together with Reymann from the Finsen Institute and eleven dermatologists in private practice involved 231 patients. The evaluation was performed by lesion counting. VAA cream was shown to be significantly better than the cream base alone. A concentration of 0.05% showed a quicker onset of action and more pronounced effect than a 0.02% concentration. In this study there was a decrease in the number of comedones and papules but not in the number of pustules or cysts. The cinical effect can be seen in pictures taken before and following 8 weeks of treatment (Figs. 1—4).

Today VAA may be used in a cream, gel, or lotion base, however, the initial studies were performed with lotion bases (5). Juhlin (9) studied the effect of 0.025% VAA in a gel. It is a common opinion (10, 11) that gel and lotion bases have a higher degree of local irritancy.

On the basis of kinetic and ultrastructural studies (12, 13) Plewig and Kligman claim that the mode of action of VAA in acne is due to: (I). Interference with comedo formation by preventing horny cells from sticking together. (II). Intensification of proliferative activity on the follicular epithelium allowing existing comedones to be unsealed and expelled and causing closed comedones to become open comedones more rapidly. (III). Allowing "blow-ups" of inapparent comedones leading to their discharge. (IV). Action as an exfoliant stimulating blood-flow and aiding in the clearance of papules and nodules. In their early reports the same authors emphasized the so-called comedolytic action and understated the activity as an exfoliant. Lately they have reevaluated their opinion of the latter — "counter irritant" effect (14).

Topical VAA has no effect on free fatty acids or on *Propionibacterium acnes* (P. acnes) (15).

There has been much discussion as to whether irritancy, i.e. redness and peeling, are necessary aspects of VAA therapy. Today it is generally felt that it is not, but the speed of the response is often improved, when VAA is used vigorously. It is extremely important that patients be given sufficient warning on irritancy reactions, and many patients may not accept the irritancy in spite of this warning. We therefore advise our patients to start using VAA on an interrupted basis and only within three weeks reach a daily dosage.

The rank order of irritancy according to Papa (11) is listed in Table 1. Other factors pertinent to VAA irritation are shown in Table 2. Hypo- and hyperpigmentation is now and then encountered, more often hypo- than hyperpigmentation. The potential for contact allergy seems low (11). There were no cases of contact sensitization in 805 men on Draize testing and in an additional 50 men is whom maximization testing

Table 1. *Rank order of irritancy of tretinoin preparations (according to Papa (11))*

	Vehicles	Tretinoin concentration
High irritation	Solution	0.05
	Gel	0.05
	Gel	0.025
	Gel	0.01
	Cream	0.10
	Gel	0.005
Low irritation	Cream	0.05

Table 2. *Factors in tretinoin irritancy (according to Papa (11))*

A. Drug
1. Vehicle
2. Concentration of tretinoin
3. Quantity applied
4. Frequency of application

B. Patient
1. Site of application
2. Method of application
3. Concomitant irritants
4. Type of skin

C. Environment
1. Temperature
2. Humidity
3. Wind
4. "Photo-irritation" — Ultraviolet light

D. Physician
1. Excessive use
2. Inadequate use
3. Concomitant topical therapy

was done. Extremely few instances of contact allergy have been reported in clinical use.

Plewig, Wolff and Braun-Falco (13) have stated that in the acute phase of VAA treatment with high concentrations (0.25%—1%) there is a psoriasiform hyperplasia of the epidermis with acanthosis, papillomatosis, loss of the granular layer, hyper- and parakeratosis, and inter- and intracellular edema with occasional exocytosis. Smaller therapeutic dosages (0.05%) lead to a pronounced granulation, and on continous use the parakeratosis disappears.

Beneficial effects have been reported from the combined use of VAA with oral antibiotics as well as with benzoyl peroxide (15). However, in the latter case, the time sequence between applications of the two drugs has to be at least 12 hours; otherwise there may be an interaction between the two drugs. Benzoyl

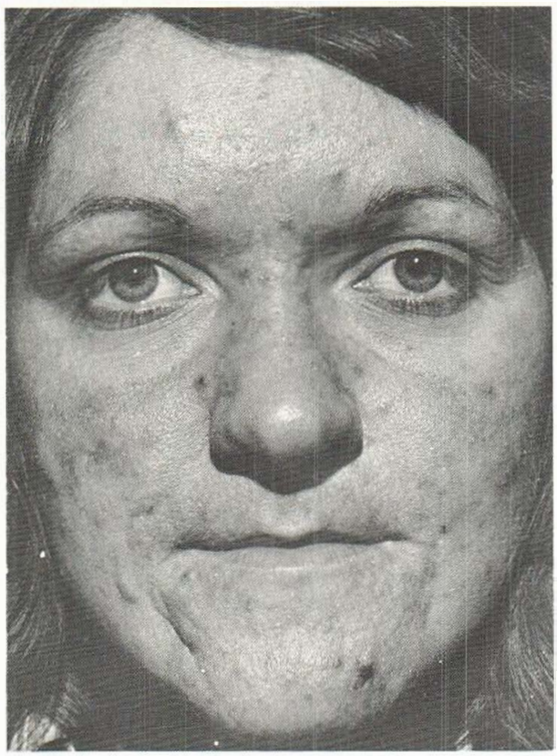

Fig. 1. Face of 22-year old girl prior to treatment.

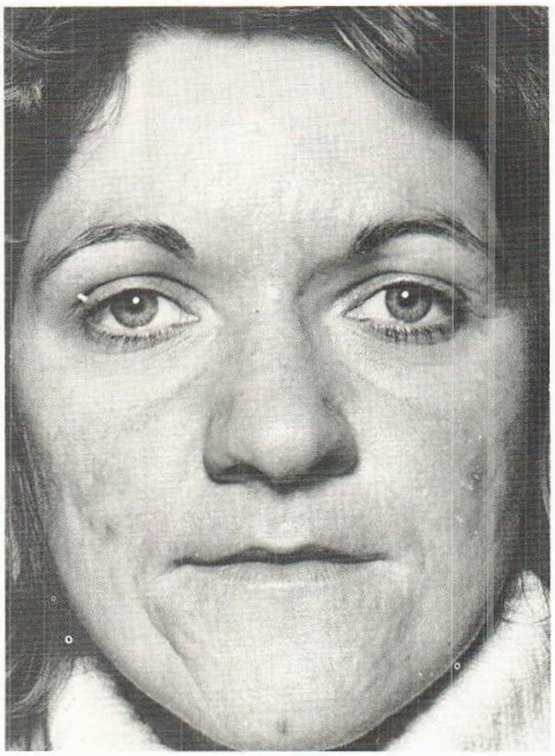

Fig. 2. Face of same patient as in Fig. 1 following eight weeks of treatment with retinoic acid cream 0.05%.

peroxide oxidizes the vitamin-A and vice versa. Normally we advise that one drug be used in the morning and the other at night.

At the International Symposium on the therapeutic use of VAA in Flims in 1977 Hjorth (16) stated "broadly speaking the indications for VAA in acne vulgaris are — acne vulgaris". I quite agree. If asked what are the indications for VAA in acne I would answer that it is the appropriate agent for almost all types of acne. The one exception is that VAA should not be used in patients with acne rosacea since the irritancy associated with VAA may flare acne rosacea.

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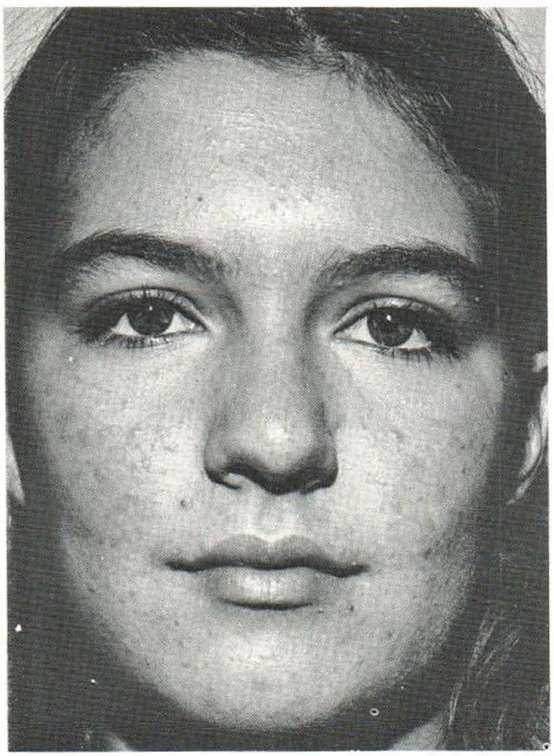

Fig. 3. Face of 17-year old girl prior to treatment.

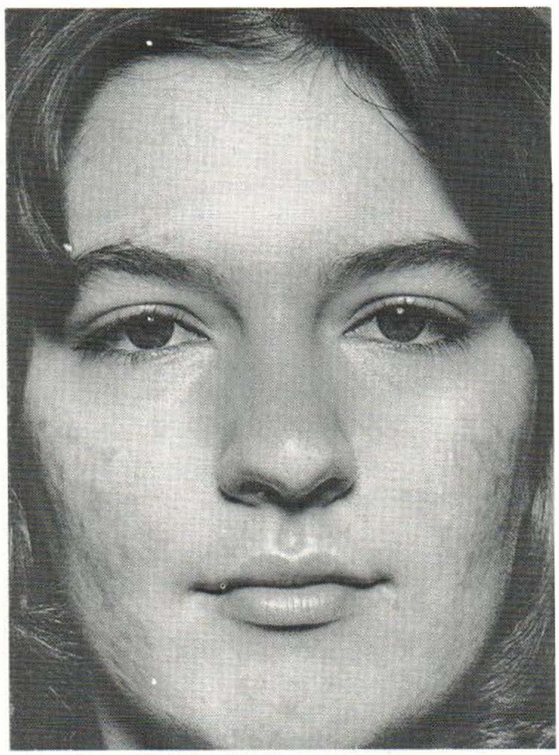

Fig. 4. Face of same patient as in Fig. 3 following eight weeks of treatment with retinoic acid cream 0.05%.

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DISCUSSION

Strauss, Iowa: I would like to discuss some new findings relative to the use of oral retinoids in cystic acne vulgaris. As you know 13-cis retinoic acid, a stereoisomer of retinoic acid, is being used in the United States for the management of patients with diseases of keratinization. An aromatic retinoid is being used in Europe for similar diseases. Dr. Gary Peck started using this compound in patients with severe cystic acne and reported excellent results. Furthermore, he has observed a protracted remission of the disease after the drug was stopped. We have collected surface lipid samples from these individuals and have found some remarkable changes, which I just like to discuss very briefly. In man there are changes in surface lipid composition in relation to age. Cholesterol, which is of epidermal origin, is found in high concentrations in children. At the time that the first stimulation of the sebaceous gland occurs at around eight years of age, the cholesterol level decreases to low levels. In contrast, the wax esters, which are uniquely of sebaceous origin, are quite low during childhood and at the same period of time, about eight years of age, the wax ester levels rise. The same can be said for squalene, which is also uniquely a sebaceous gland product. Therefore, in prepubertal individuals where more of the surface lipid is of epidermal origin, the cholesterol level is increased, while the concentration of wax esters and squalene is low. The reverse is true in adults in whom most of the surface lipid is of sebaceous origin. When patients are treated with 13-cis retinoic acid we have noted a great increase in cholesterol at the same time as the wax esters and squalene have decreased. The triglycerides, which are of dual origin, remain unchanged.

We now have sebum production values in three of these individuals, and we have found that the three values for sebum production are extremely low. We believe that there has been over a 90 per cent reduction in sebum production in these patients treated with 13-cis retinoic acid.

The dosages that have been used so far are quite high, and there have been a fair number of side effects. More studies will be required before this form of therapy becomes practical.

Cunliffe, Leeds: I am fascinated with Dr. Strauss's results with oral retinoids. Could you speculate any further than the data you have given us today? Can you suggest where this material is acting?

Strauss, Iowa: I am sorry, I cannot give you any information at all. We do not even know the optimal dosage level. I want to emphasize, however, that it is the first time we have used a suppressive agent which has caused a change in surface lipid composition. Almost all of the surface lipid of the face is of sebaceous origin. We believe that more than an 80 per cent reduction in sebum production is required to produce this change.

Zachariae, Aarhus: What about fractionated serum lipids? Do they change?

Strauss, Iowa: I do not know.

Plewig, Munich: It is usually said that benzoyl peroxide and vitamin-A-acid should not be combined. However, we have been doing this for some time. We apply both drugs, if the patient tolerates them, at the same time in the morning and the same time at night, two minutes apart. It works well. So what the chemists tell us, may not be true clinically.

Schaefer, Berlin: As I have already mentioned, vitamin-A-acid is not stable on the skin surface and perhaps you promote this disintegration. Therefore, is the active principle of topical application of vitamin-A-acid the drug itself or a metabolite. We do not know the answer to this question.

Shuster, Newcastle-upon-Tyne: I think that Dr. Strauss's compound is really very exciting. There is going to be no question about having to assess the clinical value of the drug if you drop sebum to that extent.

Juhlin, Uppsala: Dr. Strauss, did you do any histological examinations on your patients treated with retinoic acid?

Strauss, Iowa: None have been done to date.

Juhlin, Uppsala: Dr. Plewig, you stated that you have used benzoyl peroxide and retinoic acid at the same time. Would you like to comment how you applied them. Did you use gels? In what order did you apply them, and is the order of importance?

Plewig, Munich: It does not matter if you start with the vitamin-A-acid preparation or the benzoyl peroxide preparation. In the beginning, only the benzoyl peroxide lotion was available in Germany, but during the past year the gel formulation has become available. I usually start with the lotion, because it is less irritating and then I increase the concentration and finally go on to the gel formulation. I apply them about 2 or 3 minutes apart.

Cunliffe, Leeds: I would like to ask a few more questions, Dr. Strauss, do you have any information as to whether the oral 13-cis retinoic acid interferes with the pill? Even if, in the next few years 13-cis retinoic acid becomes available, are we going to be making more of our patients pregnant if there is inter-reaction with the pill?

Strauss, Iowa: I know of no information relative to the combined use of 13-cis retinoic acid and the pill, but I do not see why there should be any interaction of the nature that you have brought up.

Cunliffe, Leeds: Secondly, I would like to ask the Retin® -A experts what their feeling is about the use of Retin® -A gel and sun light? We hear lots of stories about it such as statements that you should not use it too much in the presence of decent sun light.

Plewig, Munich: Before we start treating patients with tretinoin (vitamin-A-acid) we tell them that it acts like "sunburn from the tube". We tell them that if you have one sunburn, do not get another one. In other words, we prescribe sun screens when they go skiing in the Alps in the winter time, or if they want to go to the Danish or Swedish beaches in the summer time. The skin is less protected because of the thin stratum corneum produced by topical vitamin-A-acid therapy.

Strauss, Iowa: The exaggerated sunburn is a real phenomenon that patients should know about.

Zachariae, Aarhus: I agree that patients should be warned about the reaction to sun.

Vahlquist, Uppsala: I have a few questions concerning vitamin-A-acid. Firstly, has anybody studied sebum production during topical treatment with vitamin-A-acid?

Schaefer, Berlin: We tried to follow up on sebum excretion during topical vitamin-A-acid treatment. In the first few days of treatment we did find some increase in sebum excretion. This confirms the observation of Gerd Plewig in that it is related to the expulsion of the comedo. Afterwards we had to stop the measurements because of the inflammatory effect to treatment.

Vahlquist, Uppsala: Secondly, I would like to ask Dr. Plewig a question. He told us yesterday that epidermal turnover in the follicular region of the sebaceous gland is increased in comedones. Treatment with vitamin-A-acid might further increase the epidermal turnover. What will the effect be of this increased turnover on the formation of comedones?

Plewig, Munich: Yes, we studied sebum output or secretion (Plewig, G. & Fulton, J. E.: Autoradiographische Untersuchungen an Epidermis und Adnexen nach Vitamin-A-Säure-Behandlung. Hautarzt 1972; 23:128-36) following topical application of vitamin-A-acid. We could not detect any difference in sebum secretion during treatment. At the same time we measured the labelling index of the sebaceous glands in these patients with an in vivo radioautography technique. There was no difference whatsoever. I feel this confirms the clinical observation that this compound has no gross effect on sebum secretion.

On the other hand, we were amazed to see that comedonal turnover is increased by application of vitamin-A-acid; however, at the same time the comedonal core is loosened from its bed. The comedonal core is expelled and it would appear that one action does not prevent the other one.

Vahlquist, Uppsala: Just a short comment. I think that the difference between the effect of topical vitamin-A-acid (VAA) and of oral 13-cis VAA reflects differences in the concentrations obtained at the sebaceous gland, and not really indicates differences in the mechanisms of action of the two agents. Would you comment on that?

Plewig, Munich: I think there is a misconception. The drug which is applied topically is a different compound from the drug which is taken by mouth. The drug which Dr. Strauss mentioned, and the one we have tried orally, is 13-cis retinoic acid, an aromatic retinoid (Ro 10-9359), which is a different substance from vitamin-A-acid (retinoic acid) which is applied to the skin. The oral drug has an extremely good effect upon sebaceous secretion, which Dr. Strauss mentioned. The other drug which is available on the market to everybody as Retin® -A or vitamin-A-acid does not have an effect on sebaceous secretion. Is that correct Dr. Strauss?

Strauss, Iowa: It is almost correct. The error is that the oral compound that you have used is an aromatic retinoid. The compound we have worked with is 13-cis retinoic acid, which is a stereo-isomer of retinoic acid. It is not an aromatic retinoid.

Vahlquist, Uppsala: Can I make a short comment again? I repeat that the vitamin-A activity of all the various formulations may be differently expressed in the epidermis at different concentrations. In fact, at low concentrations, the effect seems to be overall stimulating, but at higher doses you will get a cytostatic effect, resulting in inhibition of epidermal proliferation.