TOPICAL RETINOIC ACID IN THE TREATMENT OF ACNE VULGARIS

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Summary

Retinoic acid was administered in 45 patients with grade I or grade II Acne Vulgaris. In 10 patients it was compared in a clinical study to sulfur — Resorcinol Shake lotion. Good to excellent response was obtained in 22 patients (48.8%) while fair response was noted in 9 patients (20.0%). In 14 patients (31.1%) there was no change. Retinoic acid was found to be effective in reducing the number of comedones to about 68-70% in both grades of Acne. When compared with the shake lotion it was found to be more effective in reducing the number of comedones (70% with Retinoic acid compared to 50% with shake lotion).

Burning of the skin, smarting pain and irritation were the main side effects noted. 9 out of 45 patients discontinued the medication on their own as a result of side effects. This was the major problem in continuing the therapy.

Retinoic acid has a significant effect on the removal of comedones as compared to the other available methods of treatment. Whilst it has only a moderate effect, in reducing papular lesions, its effect on the pustules and cysts is virtually negligible.

Vitamin A has been used in the treatment of Acne Vulgaris since many years. Straumjform (1943) first reported apparent clinical benefits after administration of Vitamin A. This was believed to be due to reduction in follicular hyperkeratosis. Cornbleet et al (1944) however, could find no abnormality in the plasma vitamin A level of patients with Acne. Lynch (1963) did a double blind trial in which he could not find any advantage of oral administration of Vitamin A over a placebo.

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Patients with Ichthyosis, Darier's Disease, Pityriasis Rubra pilaris, Ichthyosiform erythroderma and Psoriasis were given Vitamin A by mouth. All except the patients with Psoriasis improved clinically after 2 to 3 weeks. Although the mechanism is mysterious the therapeutic efficacy of Vitamin A is not disputed. To avoid the hazards of systemic toxity many trials of the topical application of vitamin A were undertaken with either Vitamin A alcohol or its palmitate. The results of these trials were conflicting and disappointing.

Stuttgen and Von Beer (1962) appear to have been the first to apply Vitamin A acid (Retinoic acid) which is not known to occur in tissues but can be derived from oxidation in vitro from the aldehyde, which does occur naturally. These authors reported favourable results in Psoriasis and Ichthyosis

respectively. Thomson and Milne (1969) used retinoic acid in Congenital Ichthyosiform Erythroderma by a combination of oral and topical route and found considerable improvement. Frost and Weinstein (1968) reported that retinoic acid was effective in Psoriasis and many hyperkeratotic disorders like Sex-linked Ichthyosis, Lamellar Ichthyosis, Bullous Ichthyosiform Erythroderma. The common type of Ichthyosis, however, did not benefit.

Kligman et al and later Plewig (1969) carried out a trial in which they showed 0.1% retinoic acid in 95% ethyl alcohol and propylene glycol to be markedly superior to either 5% Sulphur and 3% Resorcinal in a bland lotion or 5% Benzyol peroxide as a topical treatment of acne. Pedace and Stoughton (1971) more recently showed fair to excellent response in 88.8% patients treated with retinoic acid whereas only 25% treated with placebo showed similar response. Peachy and Connor (1971) made a pilot study of 22 patients with acne who received 0.1% retinoic acid lotion ; slight to moderate improvement was noticed in 13 patients, however, the irritant effect of the lotion was a major problem producing an unacceptable degree of erythema and peeling.

The present report deals with the results obtained with the topical application of 0.05% retinoic acid in the treatment of acne vulgaris.

Materials and Methods

Fortyfive patients with typical acne lesions were selected for study. Most of them were aged between 16 to 23 years. The patients selected had predominantly comedones and papules and very few pustules. Patients having preponderance of pustules and cysts were discarded. Most of these patients attended the skin clinic for the first time and did not receive any other treatment except for the use of commercially available acne preparations. None of them received systemic antibiotic therapy.

At the first visit to the skin clinic, the patients were asked full history, treatment undertaken and a careful examination was done to type out the grade of acne. Many patients did not have lesions on back and shoulders and hence only facial lesions were considered at first and subsequent visits. All types of lesions were counted and their numbers recorded on a proforma. Before the start of treatment and at the end of trial period photographs were taken to assess the results. Majority of patients attended at weekly or fortnightly intervals and were followed up for a period ranging from 10 weeks to 24 weeks. At every visit, the comedones, papules and pustules were counted and their number recorded.

The patients were advised to use the lotion once every night after a soap and water cleaning. They were also given full explanation regarding the effects the lotion may produce. In case of irritation, they were advised to use the lotion less frequently.

Ten patients out of fortyfive also received a lotion containing 3% Resorcin and 6% sulphur in calamine lotion (B.P) for comparative studies on one side of the face.

At the end of trial patients were evaluated for overall response in which improvement was recorded in 4 categories. Excellent, if all the visible lesions were essentially cleared ; good, if the condition was greatly improved but several lesions persisted; fair, if the lesions were reduced but still troublesome; and poor, if there was no change or the disease was worse.

The formation of the lotion used was as follows:

Retinoic acid	0.05%
Polyethylene Glycol	49.90%
Denatured spirit	50.00%
Butylated hydroxy toluene	0.05%

Results

The results of treatment in 45 patients are summarised in Tables 1, 2 and 3.

TABLE 1

Overall response of treatment of acne

Type of response	No. of patients	Percentage
Excellent	10	22.2
Good	12	26.6
Fair	9	20.0
Poor	14	31.1

TABLE 2

Summary of comedones and papular counts
Total number of patients 45

	Comedones		Papules	
	No. of patients	Percentage	No. of patients	Percentage
Reduction of more than 50%	31	68.9	20	44.4
Reduction of less than 50%	14	31.1	25	55.6

TABLE 3

Retinoic Acid Vs. Shake Lotion
(Half face study)
Summary of comedone reduction
Total number of patients 10

	Retinoic Acid		Shake Lotion	
	No. of patients	Percentage	No. of patients	Percentage
Reduction of more than 50%	7	70	5	50
Reduction of less than 50%	3	30	5	50

In general, overall good to excellent response was obtained in 48.8% of patients while in 31% the response was poor. Many patients who showed poor response discontinued the lotion on account of irritation, burning or dryness of the skin.

The comedone reduction was quite marked in patients showing good to excellent response. Reduction of approximately 68% was noticed in these patients. In 20% of the patients who showed fair degree of response, comedone reduction was seen but papules were largely unaffected.

The papular reduction was not as striking as comedones and more than 50% reduction was seen in 44.4% of patients. In many instances papules did not change appreciably.

The pustules and cysts did not show worthwhile changes and in few cases they were flared up.

Another important observation was the lack of co-ordination between erythema-peeling and reduction in comedone counts. Although erythema and peeling was quite marked in majority of patients, the clinical improvement was not noticeable. There was a time lag of 2–3 weeks before the effect was appreciated.

Discussion

The results seem to indicate clearly that retinoic acid is an irritant that causes significant erythema and peeling. The mechanism how this is brought about remains speculative. Kligman et al (1969) do not think that topical effect has anything to do with its physiological effects as a vitamin but suggest that its action may be related to its capacity to labilise lysozomes, thereby releasing proteolytic and hydrolytic enzymes capable of exciting inflammatory reaction.

These effects probably increase the rate of production of loose, horny cells in the follicular canal thus preventing formation of new comedones and tending to dislodge the existing ones.

Kligman et al and more recently Pedace and Stoughton have shown high degree of cure rates with retinoic acid lotion. Both the workers, however, do not mention the degree of irritation that accompanies the treatment. In the present series overall good to excellent response was seen in 48% who were persuaded to continue the medication for a period of 12 weeks or more. Whilst there is no doubt that retinoic acid is quite effective in reducing the number of comedones upto 60–70% and to a lesser degree the papules upto 40% the amount of irritation and discomfort that accompanies to achieve these results is remarkable. Peachey and Connor had a similar experience in their pilot study and they thought that if the frequency of application is reduced to lessen the effects of irritation, the effectiveness of the lotion was also lost. In the present series 9 out of 45 patients did not return voluntarily and stopped the treatment on their own owing to side effects of treatment.

In 10 patients with half face studies, retinoic acid was found to be superior to that of shake lotion containing 6% sulphur and 3% Resorcin.

Histological studies have been observed after treatment with retinoic acid. Mcgills et al have summarised them as follows:

	Before treatment	Treatment after 12 weeks
1. Keratin layer	Normal	Reduction compared to pretreatment.
2. Epidermis	Normal	Stratum granulosum increased — marked acanthosis.
3. Basal layer	Normal	Normal.
4. Follicles	Large, plugged with keratin	Plugs absent.
5. Glycogen	Present in dermis & epidermal rete	Increased in epidermal rete and follicle cystwall.
6. Sebaceous Glands	Not present in cystic areas	Increase in size.
7. Bacteria	Present in Keratin comedo	Absent.
8. Acid muco-polysaccharide	Present in spaces within keratinous follicysts	Absent.
9. Elastic fibres	Present	Normal.
10. Hyaluronic acid	Present in keratinous follicle cysts	Decreased in amount.

Temporary loss of pigment has been observed by both Pedace and Stoughton and Mcgills et al in patients with dark pigmented skins. On cessation of treatment, pigmentation re–appeared. In none of our patients this phenomena was observed although all our patients had a variable degree of pigmentation.

Schumacher and Stuttgen tried the effects of oral retinoic acid in acne and other diseases; considerable improvement was achieved in acne vulgaris with initial daily administration of 10–20 mgm reduced to 5 mgm daily for long term use.

Much work needs to be done to find out the adequate concentration of retinoic acid which can lessen the irritation and at the same time exert an effective action on removal of comedones. Perhaps a combination of oral and topical use of retinoic acid can give us better results.

In conclusion it can be said that retinoic acid has a significant effect on the removal of comedones as compared to the other available methods of treatment. Whilst it has only a moderate effect in reducing papular lesions, its effect on the pustules and cysts is virtually negligible.

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