Differential Effect of 13-cis-Retinoic Acid and an Aromatic Retinoid (Ro 10-9359) on the Sebaceous Glands of the Hamster Flank Organ

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The effect of subcutaneously administered 13-cis-retinoic acid and an aromatic retinoid (Ro 10-9359) on the sebaceous glands of the hamster flank organ were compared. As previously reported, 13-cis-retinoic acid caused a marked diminution of sebaceous gland size without affecting other androgen dependent structures. The aromatic retinoid derivative showed no effect upon any of the flank organ components. Studies utilizing androgen stimulated female confirmed our previous finding that 13-cis-retinoic acid prevented the growth of sebaceous glands without affecting the development of dermal pigmentation or large pigmented hair follicles. The aromatic retinoid derivative showed slight, if any, effect upon sebaceous gland size and no effect upon pigmentation or pigmented follicle development. The findings with this model system suggest that any efficacy of Ro 10-9359 in the treatment of acne would be by some mode other than the inhibition of sebum production.

Two retinoids, 13-cis-retinoic acid and an aromatic retinoid derivative (Ro 10-9359) have been reported to be efficacious in disorders of epidermal keratinization [1, 2]. 13-cis-Retinoic acid has also been reported to be extremely effective in the treatment of severe cystic acne [3] and appears to exert its effect in this condition by the marked suppression of sebum production [3, 4]. 13-cis-Retinoic acid has also been shown to cause marked atrophy of the sebaceous gland but not the other androgen dependent structures of the hamster flank organ [5], a tissue that has proved useful for assaying potency of drugs, such as antiandrogens, which affect sebaceous gland growth [6–9]. We have compared the effectiveness of 13-cis-retinoic acid and an aromatic retinoid (Ro 10-9359) in producing sebaceous gland atrophy in the hamster flank organ in the hope that this assay might prove predictive of efficacy in the treatment of acne.

MATERIALS AND METHODS

Mature male Syrian hamsters purchased and caged as previously described [5] were injected subcutaneously with 13-cis-retinoic acid, the aromatic retinoid, or the vehicle. Both the 13-cis-retinoic acid and the aromatic retinoid were a gift of Hoffmann-La Roche, Inc., and were supplied as 25% concentrates in an oil vehicle (70.5% soybean oil, 0.8% beeswax, 0.8% hydrogenated soybean oil flakes, 19.4% vegetable shortening, 0.3% disodium Edetate and 0.07% butylated hydroxyanisole). The 13-cis-retinoic acid concentrate was stored under nitrogen at −20 degrees centigrade and the aromatic retinoid concentrate was stored in the dark at room temperature as per the directions of the Hoffmann-La Roche Corporation. Assay of the aromatic retinoid concentrate by the Hoffmann-La Roche Corp. two months after completion of the experiments showed that the material was indeed Ro 10-9359 and that there had been no loss in potency. Prior to injection, the 13-cis-retinoic acid concentrate was brought to room temperature by immersion of the bottle in water. The concentrates and the placebo oil were administered by subcutaneous injection at a site distant from the flank organs. Animals were injected twice each week for a period of 3 weeks. In experiments using females, 40 mg of testosterone enanthate was injected concurrently with the first administration of the retinoids or placebo. The testosterone injection was repeated weekly during the course of the experiment.

After 3 weeks of treatment, the animals were sacrificed and the flank organs removed and processed for histologic examination as previously described [5].

RESULTS

Subcutaneous administration of 13-cis-retinoic acid and Ro 10-9359 in an identical oil vehicle produced different results. Animals treated with 13-cis-retinoic acid showed a marked inhibition of sebaceous gland size as previously described [5]. Administration of Ro 10-9359 produced no change in the size of the flank organs sebaceous glands when compared to animals treated with the oil vehicle alone (Figure).

Experiments utilizing testosterone enanthate stimulated females showed a marked inhibition by 13-cis-retinoic acid of the growth of the sebaceous glands but not other androgen dependent structures of the hamster flank organ, as previously described [5]. Treatment of such animals with Ro 10-9359 showed slightly less growth of the sebaceous glands than did vehicle treated controls. The effect was slight and not noted in all animals.

DISCUSSION

Our recent studies with 13-cis-retinoic acid have demonstrated that the sebaceous glands of the hamster flank organ may be a suitable assay for the effect of the retinoids upon sebaceous glands. It appears that this effect is not present in all biologically active retinoids since an aromatic retinoid derivative (Ro 10-9359) which has shown efficacy in the treatment of psoriasis and other keratinizing disorders has little effect upon sebaceous gland growth in this system. Our assay differs from the clinical use of the retinoids, which is by oral administration. Thus, release of the retinoid from the subcutaneously injected oil vehicle or a need for metabolism or activation of the compound in the process of absorption from the gut may influence our results. 13-cis-Retinoic acid appears to present no difficulties in this regard. The lack of effect noted with Ro 10-9359 was not due to an inactive or incorrectly prepared formulation since subsequent analysis of the material used, performed by laboratories at Hoffman-LaRoche, confirmed both the identity and potency of the preparation.

We have found no published clinical reports concerning the efficacy of Ro 10-9359 in the treatment of acne or on sebum production. Our assay would predict that any effect of this compound in the treatment of acne would be by some mode other than the inhibition of sebum production.
REFERENCES


