Acta Derm Venereol (Stockh) 1987; 67: 331–335

Baseline Water Loss and Sweat Gland Response in Acne Patients During Treatment with Isotretinoin

RAIJA KIISTALA,[1] JORMA LAUHARANTA[1] and URPO KIISTALA[2]

[1]*Helsinki University Central Hospital, Department of Dermatology and*
[2]*Central Military Hospital, Helsinki, Finland*

Kiistala R, Lauharanta J, Kiistala U. Baseline water loss and sweat gland response in acne patients during treatment with isotretinoin. Acta Derm Venereol (Stockh) 1987; 67: 331–335.

Eleven acne patients were treated with isotretinoin for 3–7 months. The water barrier function and the response of sweat glands to dilute methacholine injections were examined on upper back skin at onset and at several visits during therapy. Bilaterally located test sites representing healthy skin or skin sites which were least affected by acne lesions were selected for the study. The same sites were used at each visit for assessing the parameters. Although skin dryness was a common finding on the face and arms, no significant changes in baseline water loss (BWL) rates were found on the back skin during isotretinoin treatment. Instead there was a significant increase in the sweat gland responsiveness to methacholine during isotretinoin treatment as measured by the evaporimetric technique. Furthermore, in four out of five patients the numbers of active sweat glands, counted in plastic imprints from the stimulated test sites, showed a similar increase during therapy when compared to pretreatment values. (Received September 5, 1986.)

R. Kiistala, Helsinki University Central Hospital, Department of Dermatology, Snellmaninkatu 14, SF-00170 Helsinki, Finland.

Isotretinoin (13-cis-retinoic acid) is an effective drug in severe cases of acne resistant to antibiotics (1). Its therapeutic effect involves the reduction of sebum excretion, an anti-keratinizing effect on the follicular epithelia and an anti-inflammatory action (1, 2).

Retinoids, both isotretinoin and etretinate, have profound effects on the epidermal structure and on the permeability when used in high oral doses in mice (3). Skin fragility and eczéma craquelé-like lesions are side-effects often seen in humans during oral retinoid therapy (4, 5). Occasionally, patients experience increased sweating of the skin during the therapy (2, 6, 7, 8).

The aim of the present study was to investigate the effect of isotretinoin on epidermal water barrier and on sweat gland function in acne patients.

MATERIAL AND METHODS

Patients and treatment

Nine male and two female patients with acne resistant to antibiotic therapy were included in this study. Their mean age was 22.9 years (range 14–40 yrs). None of the patients had received any local therapy or phototherapy during at least one month before examination; four patients were on tetracycline therapy at the beginning of this study. The drug was tapered and stopped within the first month (Table I). The initial dose of isotretinoin (Roaccutan®; F. Hoffman-La Roche & Co. Ltd, Basle, Switzerland) was 40–60 mg/day. The dose was reduced in two patients to 20 mg/day and in one patient to 10 mg/day by the end of the treatment period of 3–7 months. The investigation was carried out in autumn to winter in nine patients and in summer to winter seasons in two patients (no. 1 and no. 2).

Measurement of water loss and sweating

The test site was normal appearing skin or the least affected areas over the back skin bilaterally and symmetrically and approximately the same sites were tested at each visit.

The subjects rested quietly in supine position with their upper part of the body unclothed for 15 min in a normal laboratory room with the mean ambient temperature 22.9°C and mean relative humidity 34.9% (Table II). Skin temperatures of the test sites were then recorded with a thermistor (S-2A, Exacon, Taastrup, Denmark). This was followed by recording baseline water loss (BWL), and after pharmacological sweat stimulation, the peak cutaneous water loss (CWL) using an evaporimeter (EpI, Servomed, Stockholm, Sweden) (9).

Sweat stimulation was induced by intracutaneous administration of dilute methacholine (MCH) chloride (Mecholyl, Sigma) in 0.1 ml doses into symmetrical sites of back skin using 26-gauge needles. In order to avoid artefactual moisture contamination and backflow of the injected liquids the epidermis was perforated from outside the actual measuring site, the needle moved approximately 1 cm intradermally into the test site center; then first the drug was injected.

After injection the peak cutaneous water loss rate (CWL), occurring in 2–3 min, was recorded (10). The rate of evaporative sweat loss (SL) was calculated by subtracting BWL from CWL.

To obtain further information about the nature of the sweat gland response, numbers of activated sweat glands were counted in five patients using a plastic imprint technique (11). Immediately after CWL measurements a liquid dental silicone rubber material (Reprosil, De Trey, Wiesbaden, Germany) was applied on the test sites and the pore numbers of activated glands from an area of 1 cm^2 were counted.

MHC concentration in saline was kept constant at 10^{-7} g/ml. This concentration is tenfold the threshold concentration for eliciting a minimal sweat response demonstrable with the evaporimeter (12).

RESULTS

Isotretinoin had a clear therapeutic effect in all patients (previously resistant to antibiotic therapy). All patients experienced dryness of the lips and facial skin with some scaling especially during the initial months of the treatment. Four patients had dry scaly lesions on the extensor sites of arms and on the dorsum of the hands. In two of the patients the BWL recording on such scaly areas was up to five times higher than on the surrounding uninvolved skin. With bland cream the value returned to normal in three days. Three patients reported on increased general sweating during the treatment (patients 2, 7 and 11) and one patient (no. 9) occasionally had a feeling of increased thirst. None of the patients reported on impaired sweating.

Table I. *Back skin condition of the patients at start and additional drugs*

Patient no.	Age	Sex	Back skin condition at start	Additional drugs
1	17	♂	Multiple papules, pustules, scars	–
2	18	♂	Few scars, some cysts	Tetracyclin 150 mg daily/1 month
3	18	♂	Normal	Tetracyclin 1000–500 mg daily/1 month
4	20	♂	Normal	–
5	26	♂	Few pustules, scars	–
6	23	♀	Multiple papules, pustules, cysts	Cyproterone acetate containing preventive pills
7	22	♀	Dry skin (atopic)	Cyproterone acetate containing preventive pills
8	14	♂	Normal	–
9	24	♂	Papules, cysts, scars	–
10	39	♂	Pustules, scars	Tetracyclin 250 mg daily/2–3 weeks
11	30	♂	Normal	Tetracyclin 250 mg daily/2 weeks

Table II gives BWL and corresponding SL data before therapy and at each visit during therapy. The individual data are averages of duplicate recordings. Table II also gives data on experimental ambient conditions and on local skin temperatures.

The BWL values did not show any consistent changes during the treatment. They were higher than previously reported on back skin in healthy controls (13). The difference in our series is at least partly due to higher skin temperatures, leading to higher evaporation rates (9).

Compared to pretreatment value the SL values increased in all but one patient (no. 1). The increase in the mean SL from 53.9±35.5 g/m^{2}h to 95.5±26.1 g/m^{2}h occurred already after 3–6 weeks of treatment. No constant further increase in SL was observed at later visits. The mean SL calculated from the individual data obtained at each time point during treatment (89.7±28.6) was significantly higher ($p<0.01$; paired t-test) than the mean SL before therapy.

Table III shows in five patients SL values and the corresponding active sweat gland numbers on the same test sites. The increases in the two parameters were fairly parallel in

Table II. *Baseline water loss (BWL) and peak sweat loss (SL) rates (g/m^{2}h) on the back skin before and during isotretinoin treatment*

Each value is the average of duplicate recordings obtained from two symmetrically located test sites. The ambient experimental conditions and skin temperatures are indicated

Patient no.	Sex	Pretreatment		3–6 weeks		2–3 months		4–5 months	
		BWL	SL	BWL	SL	BWL	SL	BWL	SL
1	♂	13	123	11	84	10	71	11	80
2	♂	14	76	10	115	15	76	14	93
3	♂	13	86	11	111	9	–	13	117
4	♂	12	72	9	113	10	137	11	132
5	♂	13	57	12	101	11	46	11	50
6	♀	12	39	9	117	9	76	–	–
7	♀	13	1	11	34	12	32	8	32
8	♂	13	43	16	121	14	127	8	135
9	♂	13	21	15	98	15	39	–	–
10	♂	11	13	11	67	8	91	–	–
11	♂	10	62	10	90	7	115	–	–
Mean		12.5[a]	53.9[a]	11.4	95.5[a]	10.9	81.0	10.9	91.3
± SD		±1.1	±35.5	±2.2	±26.1	±2.8	±36.6	±2.3	±40.0
Median:			57		101		76		93
Room temperature (°C) Mean ± SD		22.1 ±0.7		23.4 ±0.9		22.5 ±1.0		22.6 ±0.9	
Relative humidity (%) Mean ± SD		40.1 ±7.8		36.6 ±4.9		32.0 ±12.7		32.4 ±11.5	
Local skin temperature (°C) Mean ± SD		34.1 ±0.5		34.4 ±0.7		33.9 ±0.7		34.2 ±0.3	

[a] BWL and SL data for comparison; recorded from back skin of healthy young men (conscripts, n=24) using the same evaporimetric method and methacholine concentration (10^{-7} g/ml, i.c. dose 0.1 ml) (Kiistala R, 1982, unpublished): BWL = mean 7.5±(SD) 2.0, median 6.8 g/m^{2}h; SL = mean 72.2±(SD) 30.6, median 69.0 g/m^{2}h.

all but one patient (no. 11) whose active sweat gland number did not change from the relatively high pretreatment value. There was a statistically significant correlation ($r=0.87$, $p<0.001$) between SL values and the numbers of active sweat glands at the same test sites.

DISCUSSION

Baseline water loss

Our study showed that no systemic changes occurred in the baseline evaporative water loss (BWL) from the back skin surface during oral isotretinoin therapy when daily doses of 40–60 mg were used. This is consistent with the findings obtained with etretinate in various dermatological disorders (14). Our measurements were confined to the least affected skin sites of back skin avoiding sites of gross acne lesions, scars or any other rashes.

On the other hand, local dryness of the skin during isotretinoin therapy is a common side-effect on other predilectional skin areas outside face and neck, such as dorsal aspect of the upper extremities. The retinoid dermatitis may be psoriasisform or mimick "eczéma craquelé" (5). Epidermal fragility on such scaly patches may lead to BWL values up to five times as high as normal (see Results).

Sweating repsonse

The significance of sweating as an aggravating factor in acne has been suggested (15, 16). Topically applied anticholinergics (17) and anhydrous aluminum chloride, possessing inhibitory effect on sweating (16) have been reported to exert some beneficial therapeutic effect on acne. Sweating is a fairly rare side-effect in patients on isotretinoin (2) but common in patients receiving etretin therapy (6).

Isotretinoin had a clear therapeutic effect on acne without any inhbitory effect on sweating. We found a significant increase in mean sweat response to methacholine stimulation after 3–6 weeks of isotretinoin therapy using the evaporimetric technique. A similar trend was observed with the plastic imprint technique. Three of the eleven patients reported on subjective experience of increased, but not disturbing general sweating.

The mechanism of the increased pharmacological responsiveness of the sweat glands during isotretinoin therapy is unclear. However, the increase in number of active sweat glands roughly parallelled the increase in sweat rates measured by evaporimetry. This demonstrates that the number of activated glands was increased. In individual glands the sweat output was probably less markedly stimulated. The increased number of active sweat glands may be the result of the keratolytic and anti-keratinizing action of retinoids on terminal portions of the sweat ducts. Removal of swollen keratin and lipoid material

Table III. *Mean evaporative sweat loss (SL) levels g/m²h and corresponding numbers of active sweat glands/cm² measured consecutively at the same test sites after MCH stimulation*

	Pretreatment		3–6 weeks		2–3 months		4–5 months	
Patient no.	SL g/m²h	Sweat glands/cm²	SL g/m²h	Sweat glands/cm²	SL g/m²h	Sweat glands/cm²	SL g/m²h	Sweat glands/cm²
7	1	2	34	10	32	9	32	15
8	43	11	121	32	127	27	135	45
9	21	6	98	31	39	24	–	–
10	13	11	67	30	91	27	–	–
11	62	29	90	30	115	25	–	–

from sweat pores may have enhanced the delivery of sweat to the skin surface during therapy in our patients. At least such a possibility is feasible in the light of our previous data concerning young healthy men who showed slightly higher sweat rates than our present acne patients before isotretinoin therapy (Table II). Interestingly, one of our female acne patients, suffering additionally from symptoms of atopic dry skin did show marked hypohidrosis which also improved to some extent during retinoid therapy (patient 7, Table II).

In support for this mode of retinoid action, reversal of poral closure has been thought as one mechanism accounting for the improvement hidradenitic lesions by isotretinoin (1). Similarly, in disorders of keratinization shedding of hyperkeratotic flakes by retinoid therapy can lead to improved ability to sweat (18) although in more severe cases sweat duct obstruction persists as demonstrated by us, even after 10000-times stronger methacholine injections than used here (10).

REFERENCES

1. Peck G, Olsen T, Butkus D, Pandya M, Arnaud-Battandier J, Gross E, Windhorst D, Cheripko J. Isotretinoin versus placebo in the treatment of cystic acne. J Am Acad Dermatol 1982; 6: 735–745.
2. Plewig G, Wagner A, Nikolowski J, Landthaler M. Effects of two retinoids in animal experiments and after clinical application in acne patients: 13-cis-retinoic acid Ro 4-3780 and aromatic retinoid Ro 10-9359. In: C Orfanos, O Braun-Falco, E Farber, C Grupper, M. Polano, R Schuppli, eds., Retinoids. Advances in Basic Research and Therapy. Berlin, Springer-Verlag, 1981; 219–235.
3. Elias P, Fritsch P, Lampe M, Williams M, Brown B, Nemanic M, Grayson S. Retinoid effects on epidermal structure, differentiation, and permeability. Lab Invest 1981; 44: 531–540.
4. Neild V, Moss R, Marsden R, Sanderson K, Fawcett H. Retinoid-induced skin fragility in a patient with hepatic disease. Clin Exp Dermatol 1985; 10: 459–465.
5. Taieb A, Maleville J. Retinoid dermatitis mimicking "Eczéma craquelé". Acta Derm Venereol (Stockh) 1985; 65: 570.
6. Camenzind M, Geiger J, Saurat J. Clinical efficacy of Ro 10-1670, the main metabolite of Tigason. In: J Saurat, ed., Retinoids: New Trends in Research and Therapy. Retinoid Symposium, Geneva, 1984. Basel, Karger, 1985; 305–308.
7. Lassus A. Systemic treatment of psoriasis with an oral retinoic acid derivative (Ro 10-9359). Br J Dermatol 1980; 102: 195–202.
8. Lauharanta J, Juvakoski T, Lassus A. A clinical evaluation of the effects of an aromatic retinoid (Tigason®), combination of retinoid and PUVA, and PUVA alone in severe psoriasis. Br J Dermatol 1981; 104: 325–332.
9. Nilsson G. Measurement of water exchange through skin. Med Biol Eng Comput 1977; 15: 209–218.
10. Kiistala R, Lauharanta J, Kanerva L. Transepidermal water loss and sweat gland response in lameller ichthyosis before and during treatment with etretinate: report of three cases. Acta Derm Venereol (Stockh) 1982; 62: 268–270.
11. Sutarman, Thomson M. A new technique for enumerating active sweat glands in man. J Physiol 1952; 117: 51P.
12. Kiistala R, Kiistala U, Kolari P, Parkkinen M. Stimulated local sweating response in atopic dermatitis. Abstracts, XVI Congressus Internationalis Dermatologiae, Tokyo, 1982; 322.
13. Werner Y, Lindberg M. Transepidermal water loss in dry and clinically normal skin in patients with atopic dermatitis. Acta Derm Venereol (Stockh) 1985; 65: 102–105.
14. Marks R, Finlay A, Nicholls S, Barton S. The effects of retinoids on stratum corneum. Structure and function. In: C Orfanos, O Braun-Falco, E Farber, C Grupper, M Polano, R Schuppli, eds., Retinoids. Advances in Basic Research and Therapy. Berlin, Springer-Verlag, 1981; 77–83.
15. Cunliffe W, Cotterill J. The Acnes, Clinical Features, Pathogenesis and Treatment. London, WB Saunders, 1975.
16. Hurley H, Schelley W. Special topical approach to the treatment of acne. Suppression of sweating with aluminum chloride in an anhydrous formulation. Cutis 1978; 22: 696–703.
17. Cartlidge M, Burton J, Shuster S. The effect of prolonged topical application of an anticholinergic agent on the sebaceous glands. Br J Dermatol 1972; 86: 61–63.
18. Baden H, Buxman M, Weinstein G, Yoder F. Treatment of ichthyosis with isotretinoin. J Am Acad Dermatol 1982; 6: 716–720.