

EFFECT OF FLUCINOLONE ACETONIDE CREAM ON HUMAN SKIN BLOOD FLOW

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Blood flow rate was measured in the forearm skin of human subjects exposed to ultraviolet irradiation. Blood flow was determined by the ^{133}Xe disappearance technique 18 hr after ultraviolet (UV) irradiation with a Westinghouse RS sunlamp held 10 inches from the skin for 10 min. Ultraviolet irradiation caused skin blood flow to increase. Application of fluocinolone acetonide cream, 0.025%, 4 times in the 16 hr following UV irradiation had no effect on either control skin blood flow or the UV-induced hyperemia.

Ultraviolet irradiation of human skin which results in erythema is associated with an increased rate of skin blood flow as measured by the ^{133}Xe injection technique [1]. Ultraviolet (UV)-induced hyperemia in dog skin [2] and guinea-pig skin (unpublished observations) is reduced by topical application of fluocinolone acetonide solution. This study in man assessed the effect on skin blood flow of 4 applications of fluocinolone acetonide cream, in the first 16 of the 18 hr between ultraviolet irradiation and blood flow determination. Fluocinolone was applied both to normal control skin and skin that had received UV irradiation.

MATERIALS AND METHODS

These experiments were conducted on the forearm skin of 17 Caucasian subjects of both sexes who were between 21 and 30 years of age. They had no known skin disease and gave no history of unusual reaction to sunlight. The skin of the volar aspect of one forearm was exposed to a Westinghouse RS sunlamp for 10 min with the face of the lamp 10 inches from the skin surface. The skin was not prepared for UV irradiation in any way. Of the 17 subjects, 5 did not exhibit erythema in the UV-exposed skin when they were studied 18 hr after UV exposure. Thus the subjects are presented in two groups, according to whether or not they developed erythema.

Fluocinolone acetonide cream, 0.025%, was applied to an area (1-2 in.²) of skin of the volar aspect of both the control forearm, which had not received UV treatment, and a similar area within the UV-treated zone on the other forearm. The fluocinolone cream was applied 4 times in the first 16 of the 18 hr between UV treatment and flow determination. The first application occurred immediately after the UV treatment; the last application occurred 2 hr prior to blood flow determination. The skin was not occluded, covered, or otherwise prepared or treated in any way before or after fluocinolone application. Blanching of the treated skin was not observed.

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Thus, in both the group that developed UV erythema and the group that did not, there are four subgroups: (1) untreated skin, (2) fluocinolone-treated skin, (3) UV-treated skin, and (4) UV- and fluocinolone-treated skin. Skin blood flow and temperature were determined in each of the 4 skin sites 18 hr after UV exposure and 2 hr after the last fluocinolone application.

Skin temperature was determined by a thermistor applied to the skin surface. Skin blood flow was determined by measuring the rate of disappearance of ^{133}Xe injected into the skin adjacent to the location of the thermistor.

The skin was prepared for injection of the xenon solution by lightly cleansing with an alcohol sponge as soon as the patient entered the room. The site was then covered with a dry sterile gauze sponge while the subject lay quietly for 15 min in the supine position until skin temperature was stable. The room temperature was $21.5 \pm 0.5^\circ\text{C}$. Skin blood flow was determined from the initial rate of disappearance of gamma radiation emitted by ^{133}Xe dissolved in sterile pyrogen-free saline. Thirty millicuries of ^{133}Xe in 0.02 to 0.03 ml were injected into the skin with a 30-gauge needle and Hamilton microsyringe [3]. The formula $F/V = \ln 2 \cdot \lambda \cdot 100/t_{1/2}$ was used to compute the flow rate; F is flow (ml/min), V is volume (ml) and may be taken as weight (gm) on the assumption that tissue-specific gravity is 1. Lambda (λ) is the xenon blood-tissue partition coefficient, taken to be 0.7, and $t_{1/2}$ is the half-time of the initial slope of the logarithm of count rate vs time. Flow rate is expressed as ml/min/100 gm of tissue.

RESULTS

The results are presented in the Table. There are two groups of subjects; those who developed UV erythema and those who did not. In each group there are four subgroups; control, fluocinolone, UV, and fluocinolone plus UV. Group 1, which developed UV erythema, also developed hyperemia and elevated skin temperature. Group 2 did not develop UV erythema nor increased blood flow or temperature.

Fluocinolone acetonide did not alter skin color, blood flow, or temperature in either normal or UV-treated skin whether UV erythema developed or not. Control skin blood flow values in Groups 1 and 2 were not different.

TABLE. Effect of fluocinolone acetonide cream and ultraviolet irradiation on skin blood flow and temperature

			Control	Fluocinolone acetonide	Ultraviolet irradiation	Ultraviolet irradiation and fluocinolone
Group 1: Developed ultraviolet erythema	Number	$\bar{x} \pm \text{SEM}$	12	12	12	12
	Blood flow (ml/-min/100 gm)	$\bar{x} \pm \text{SEM}$	14.7 \pm 1.8	14.0 \pm 1.7	35.4 \pm 4.2 ^a	36.7 \pm 4.1 ^a
Group 2: Did not develop ultraviolet erythema	Temperature (°C)	$\bar{x} \pm \text{SEM}$	30.9 \pm 0.3	31.0 \pm 0.3	32.3 \pm 0.4 ^b	32.2 \pm 0.3 ^a
	Number	$\bar{x} \pm \text{SEM}$	4	4	5	5
Group 2: Did not develop ultraviolet erythema	Blood flow (ml/-min/100 gm)	$\bar{x} \pm \text{SEM}$	16.2 \pm 2.0	16.2 \pm 3.8	16.4 \pm 4.4	15.2 \pm 6.8
	Temperature (°C)	$\bar{x} \pm \text{SEM}$	30.8 \pm 0.6	30.5 \pm 0.4	30.3 \pm 0.6	30.0 \pm 0.7

Significantly different from control: a, $p < 0.001$; b, $p < 0.025$.

Because we have frequently observed that there is a slight delay between injection of xenon in saline into the skin and the onset of the initial fast portion of the xenon disappearance curve, we have done a statistical analysis of the duration of that delay to assist other investigators who may want to use this method. For $n = 133$ determinations, including those previously reported [1], the range of the delay was 0 to 1.1 min. The mean delay was 0.25 min, ± 0.02 SEM. When the determinations were divided according to whether erythema was present or absent, there were 63 with UV erythema and 70 without erythema. The 70 without erythema have significantly longer delay and lower flow rate and temperature than the 63 with erythema, $p < 0.001$. For the nonerythema group the delay was 0.32 ± 0.04 min, the flow rate was 15.0 ± 0.8 ml/min/100 gm, and the temperature was $30.4 \pm 0.1^\circ\text{C}$ (mean \pm SEM). For the erythema group the delay was 0.17 ± 0.03 min, the flow rate was 30.5 ± 1.5 ml/min/100 gm, and the temperature was $32.2 \pm 0.2^\circ\text{C}$ (mean \pm SEM).

DISCUSSION

Ultraviolet (UV) irradiation which resulted in erythema was accompanied by increased skin blood flow rate and skin temperature as previously reported [1]. Variation in the response to the sunlamp is probably accounted for on the basis of seasonal (summer) protection by melanin from the erythemogenic effects of this low UV dose. No attempt was made to protect the UV-exposed skin by a sunscreen or other agent.

Fluocinolone acetonide cream, 0.025% applied topically 4 times in 16 hr, did not influence skin blood flow in either normal skin or skin with UV-induced erythema and hyperemia. There are several possible explanations of this result. It may be that fluocinolone acetonide does not affect skin blood flow. This is not likely because its potency is assayed by blanching of skin [4] and because a solution of fluocinolone acetonide decreased skin

blood flow when it was applied for 48 hr to dog skin with UV erythema-hyperemia [2] and for 24 hr to guinea-pig skin with UV erythema-hyperemia (unpublished observations) and for 48 hr to normal dog skin [2]. Blanching was never observed. Fluocinolone is capable of reducing skin blood flow in the dog and guinea pig but it did not do so in man. Perhaps, the fluocinolone is more effective when it is in solution in propylene glycol than when it is in the cream. Perhaps 16 hr is not enough time for the agent to act. Perhaps application by the subject is not as dependable as application by the investigator (dogs, guinea pigs). If who applies the agent is the critical variable, this could have a profound effect on home treatment regimens. In another study, flurandrenolide dispersed in the adhesive layer of tape, applied continuously for 24 hr did reduce human skin blood flow [5]. This difference may be due both to the vehicle and mode of application. Although 0.2% fluocinolone acetonide cream, 8 times the concentration used in this study, applied under occlusion on normal human skin for 6 days did not alter blood flow; it did alter blood flow within 6 to 8 hr on stripped skin [6]. Thus, failure to observe reduction of skin blood flow in this study suggests that fluocinolone acetonide was not absorbed.

Although it is never satisfactory to claim species difference to account for differences of results, it is perhaps true that shaving the experimental animals in some way prepared the skin for fluocinolone absorption (although the diffusion barrier for xenon, i.e., the stratum corneum, remained intact). Perhaps because the human subjects have eccrine sweat glands which the experimental animals do not, and because of the wiping action of clothing and bed sheets, the cream was removed from human skin. Again, if these reasons are important in explaining this difference, they would also be important in the evaluation of therapeutic application of these agents.

Control skin blood flow and temperature in these

two groups of subjects did not differ from the control flow and temperature of the earlier group studied under similar laboratory conditions, 14.2 ± 1.4 ml/min/100 gm (mean \pm SEM), and $30.2 \pm 0.2^\circ\text{C}$, (mean \pm SEM) [1]. UV-induced erythema was again associated with significant elevation of skin blood flow and temperature [1]. These findings support the reproducibility of the technique [1-3].

The delay in onset of the fast initial phase of flow has been characterized. It probably is the result in part of local increase in tissue pressure which results from suddenly depositing 0.02 to 0.03 ml saline within it, and of the temperature difference ($\geq 8^\circ\text{C}$) between skin, $\geq 30^\circ\text{C}$, and saline at room temperature, $21.5 \pm 0.5^\circ\text{C}$. This is corroborated by the shorter delay in the faster flow situation which undoubtedly allows for much more rapid equilibration of tissue pressure and temperature.

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