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DICHOTOMY IN RESPONSE TO INDOMETHACIN IN UV-C and UV-B INDUCED ULTRAVIOLET LIGHT INFLAMMATION

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In subjects irradiated with both UV-C and UV-B ultraviolet light (UVL), 10 μg of intradermal indomethacin decreased the redness in all 13 of the UV-B irradiated areas but in only 2 of 13 of the UV-C irradiated areas. Higher doses of intradermal indomethacin (50 μg and 100 μg) decreased the redness produced by UV-C irradiation in 6 subjects. It is suggested that the failure of 10 μg of indomethacin to decrease the redness of the UV-C induced inflammation, while decreasing the redness in the UV-B induced inflammation, is consistent with the possibility that prostaglandins participate in UV-B but not UV-C induced inflammation.

It is well known that two distinct regions of the ultraviolet light (UVL) spectrum, 250 nm (UV-C range) and 297 nm (UV-B range) have great efficiency in producing inflammation in human skin. Ultraviolet radiation from other regions of the spectrum produce much less skin inflammation [1,2]. The inflammation produced by 250 nm UVL is distinct from that produced by 297 nm UVL. The former is less intensely red, develops and fades more rapidly, does not produce blisters, and, unless given in high doses [3], does not increase pigmentation [1]. Rottier and Mullink [4] proposed the existence of two mediator substances to explain the differences observed in their studies of 297 nm and 250 nm UVL induced inflammation, while van der Leun [5] concluded that 250 nm induced inflammation was produced by a direct effect of 250 nm photons on dermal capillaries and 297 nm induced inflammation was produced by a diffusable vasodilating substance.

Intradermal injection of the prostaglandin (PG) synthetase inhibitors, aspirin and indomethacin, delay and decrease the inflammation induced in human skin by irradiation with lamps producing 297 nm (UV-B) UVL [6]. Topical indomethacin blanches human skin reddened by natural sunlight and UV-B-emitting lamps [7]. These findings support the evidence suggesting that certain prostaglandins are important mediators of the inflammatory response to UV-B [8,9].

The current study was designed to evaluate the effect of intradermal indomethacin on UV-C induced inflammation in human skin.

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MATERIALS AND METHODS

Ultraviolet light irradiation. Two Westinghouse FS-20 sun tubes (major emission 290–320 nm; intensity 2,000 μw/cm² at 10 cm) were the light source for the UV-B in this study. A Westinghouse Sterilamp 782L-30 (major emission 250 nm; intensity 1200 μw/cm² at 10 cm) was the source for the UV-C. Spectrographic studies employing a McPherson Vacuum Ultraviolet Monochromator (McPherson Corporation Model #235) confirmed the emission spectra of these lamps. The Sterilamp was "aged" for 100 hr before experiments were begun, and was "warmed-up" for at least 20 min before each experiment.

Thirteen healthy, informed dermatology residents and faculty (8 men and 3 women, ages 20 to 39 years) received between 3 and 5 times their average minimal erythema dose (MED) from the Sterilamp (UV-C lamp) to a 6 × 2.5 cm rectangular area on the volar forearm and between 3 and 5 times their average MED from the FS-20 (UV-B) lamp to a nearby 6 × 2.5 cm rectangular area on the same volar forearm. The MED with the UV-C lamp was determined 8 hr following exposure and with the UV-B lamp 24 hr following exposure. Six additional, informed dermatology residents and faculty (4 men and 2 women, ages 25 to 40 years) received between 3 and 5 MEDs of UV-C to a 6 × 2.5 cm rectangular area on the volar forearm.

Intradermal injections. Immediately after irradiation, 10 μg of indomethacin suspended in 0.05 ml of neutral sterile saline (0.9%) and a control of 0.05 ml of neutral sterile saline (0.9%) were injected intradermally into separate sites in the UV-C and UV-B irradiated areas of the 13 volunteers (Fig.). Doses of 50 μg and 100 μg of indomethacin suspended in 0.05 ml neutral sterile saline (0.9%) and a 0.05 ml saline control were injected into separate sites of the UV-L irradiated area of the 6 additional volunteers irradiated with UV-L only.

The injections were considered intradermal only if a "peau d'orange"-appearing wheal was produced. To minimize possible regional variation the injection sites were randomized.

Grading system. Following irradiation and injection of indomethacin and saline, the irradiated sites were observed for development of redness. The degree to which redness at the irradiated, injected sites differed from the irradiated, noninjected sites was graded on a 0 to +3

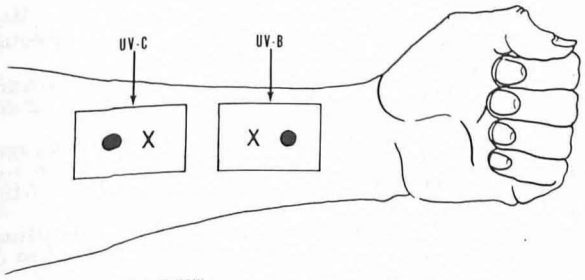

FIG. Diagram of experimental design.

scale: 0 = redness equal to noninjected irradiated sites, +1 = slightly less red than noninjected, irradiated sites, +2 = clearly less red than noninjected, irradiated sites, and +3 = equivalent to color of nonirradiated, adjacent forearm skin. To be considered a positive response, the indomethacin injection site had to be less red than the control saline injection site.

RESULTS

The response of the skin to irradiation with UV-C was clearly different from the response to irradiation with UV-B. The areas irradiated with UV-C became red in 1 to 2 hr after irradiation, were a pink or light-red color, returned to normal skin color within 24 hr, and did not become tanned or hyperpigmented. The areas irradiated with UV-B became red 3 to 5 hr following irradiation, were a scarlet or deep-red color, remained red for over 2 days, and became tanned.

Redness was decreased in all 13 volunteers irradiated with UV-B and injected with 10 μg of indomethacin when compared to the adjacent, noninjected skin irradiated with UV-B. The decreased redness was noted when the irradiated, noninjected sites became red (3 to 5 hr after irradiation). The areas of decreased redness were approximately 1 cm in diameter and reached a 2.5 degree of decreased redness. Five to six hours after their appearance these areas were as red as the adjacent, irradiated, noninjected areas. The control saline injection had no effect on the development of redness in the UV-B irradiated area. In 11 of the 13 volunteers, indomethacin (10 μg) had no effect on the development of redness in the UV-C irradiated areas or a similar brief delay in the development of redness was observed at both the saline control and indomethacin injected sites. In 2 volunteers redness was decreased at the UV-C irradiated site injected with 10 μg indomethacin in 0.05 ml of saline. These areas of decreased redness were apparent when the adjacent area became red, were approximately 1 cm in diameter, reached a +1 degree of decreased redness, and became as red as the adjacent UV-C irradiated skin in approximately 2 hr.

The UV-C redness was decreased in all of the volunteers injected with 50 μg of indomethacin and in 5 of the 6 injected with 100 μg of indomethacin (Tab.). The maximum degree of decreased redness was noted approximately 1½ hr after the UV-C redness first developed.

DISCUSSION

In the 13 subjects irradiated with both UV-B and UV-C, 10 μg of indomethacin intradermally decreased the redness in all of the UV-B irradiated areas, but in only 2 of the UV-C irradiated areas. Higher doses of intradermal indomethacin decreased the redness of UV-C irradiated skin in all of the subjects tested. In earlier studies 5 μg of intradermal indomethacin reduced the redness of UV-B induced inflammation [6].

Although not proved, it has been suggested that indomethacin affects UVL-induced inflammation by inhibiting the prostaglandin synthetase system. In addition to its effect on the PG synthetase enzyme system, indomethacin is known to affect prostaglandin 15'dehydrogenase [10], phosphodiesterase [11], dopa decarboxylase [12], oxidative phosphorylation [13], and histidine decarboxylase [14]. Other effects of indomethacin include inhibition of leukocyte motility [15], inhibition of urate binding to albumin [16], stabilization of proteins [17] and erythrocyte membranes [18], and inhibition of enzyme release from lysosomes [19]. The concentration of indomethacin necessary to produce these effects varies widely and is generally far higher than the concentrations necessary to inhibit the prostaglandin synthetase system (reported with 0.17 μM concentrations) [20].

Assuming the indomethacin injected intradermally is distributed within 1 gm of tissue which approaches 1 ml (considering the size of the wheal raised by our injection) the 10 μg injection produces an estimated 0.28 μM concentration of indomethacin. The 50 μg and 100 μg injections produce estimated concentrations of 1.4 and 2.8 μM, respectively. All of the concentrations are probably sufficient to inhibit the PG synthetase system.

The failure of the 10 μg dose of indomethacin to decrease the redness of UV-C induced inflammation, while decreasing the redness in the UV-B induced inflammation, is consistent with the possibility that PG is an important mediator of UV-B but not UV-C induced inflammation. The ability of high doses of intradermal indomethacin to

TABLE. *Effect of intradermal indomethacin on UVL-induced redness*

The average decrease in redness at each dose was determined by dividing the sum of the scores at each test site by the number of areas with decreased redness.

Dose (μg)	No. of sites tested	No. of areas with decreased redness	Average decrease in redness	Average duration of decrease (hr)
10	13	2	1	2
50	6	6	2	2.8
100	6	5	1.8	2.4

reduce the redness of UV-C induced inflammation is consistent with the known capacity of indomethacin to affect many systems in higher concentrations which are not affected by indomethacin in lower concentrations.

As UV-B and UV-C inflammation are clinically distinct, it seems reasonable that the endogenous mediators of these inflammatory reactions may differ. One should anticipate a host of pharmacologic and biochemical dissimilarities in addition to the photobiologic dissimilarities between UV-B and UV-C induced inflammation. It is important to define the UVL source used in experimental models employing UVL-induced inflammation. Defining the UVL source is especially critical when information generated in the laboratory is used to explain the effects of terrestrial UVL (which does not contain 254 nm UVL).

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