UVB Erythema Inhibited by Topically Applied Substances

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The photoprotective and antierythematous effects of topical corticosteroids, acetylsalicylic acid (ASA), indomethacin (IM), butylhydroxytoluene (BHT) and diphenhydramine hydrochloride (DPH) and the influence of the application time on the formation of erythema were studied in healthy volunteers. The test substances, incorporated in o/w creams, were applied to the back in large Finn Chambers® 24, 4 and 1 hours before and 1 and 4 hours after ultraviolet light B (UVB) irradiation (3×MED). The reactions were assessed both visually and using a laser Doppler flowmetry device. When applied before irradiation, ASA and IM, significantly inhibited UVB erythema. When applied after irradiation, IM, DPH and potent corticosteroids reduced UVB erythema, but ASA, BHT and hydrocortisone did not. 5% ASA had the greatest photoprotective effect when the cream was applied 4 hours or 1 hour before irradiation. The photoprotective effect was only slight when the 5% ASA cream was applied 24 hours before irradiation. *Key words: Anti-inflammatory agents; Antihistamine; Antioxidant; Laser Doppler flowmetry; Chamber test.* (Accepted August 10, 1988.)

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Erythema appears within two to three hours, reaches its maximum within 8–24 hours and fades away within 24–48 hours of exposure to ultraviolet light B (UVB) (280–320 nm) (1–3). In previous experiments, many of them performed on animal skin (6, 7, 10, 11, 13, 17, 21), steroid anti-inflammatory drugs (4, 6, 9, 10, 12, 14), nonsteroid anti-inflammatory drugs (5–10, 12, 15, 17–19), antioxidants (11, 13, 21) and antihistamines (16, 20) have been found to have effect on UVB erythema formation.

In the present study, we investigated the effects of topically applied corticosteroids, acetylsalicylic acid, indomethacin, an antioxidant (butylhydroxytoluene) and an antihistamine (diphenhydramine) on UVB erythema in human skin using a standardized chamber application test technique that enables testing of more than 50 substances at the same time.

MATERIAL AND METHODS

Test persons

Ten Caucasian volunteers, four females and six males aged 30–72 years, participated in the study. The subjects were untanned, had normal tolerance to UV light and were not taking betablockers, anti-inflammatory medication (steroidal or non-steroidal) or antihistamines.

Test substances and UVB source

Unless otherwise stated, the test substances were incorporated in an o/w cream which contained 65% water, 8% glycerol and 27% Lanette® N (Henkel KGaA, Düsseldorf, FRG) (Table I). The UVB light source was a microprocessor-monitored Waldmann UV 6002 apparatus (Herbert Waldmann GmbH+Co, Villingen-Schwenningen, FRG) with 40 Sylvania F 75/85W UV6 tubes (USA) and a maximum output of 311 nm. The UVB dose was 3×MED (0.29–1.14 J/cm^2).

Course of the study

We used large Finn Chambers® (Epitest Ltd, Hyrylä, Finland) with an inner diameter of 12 mm on Scanpor® acrylic tape (Norgesplaster A/S, Oslo, Norway). They were filled with 50 mm^3 doses of the

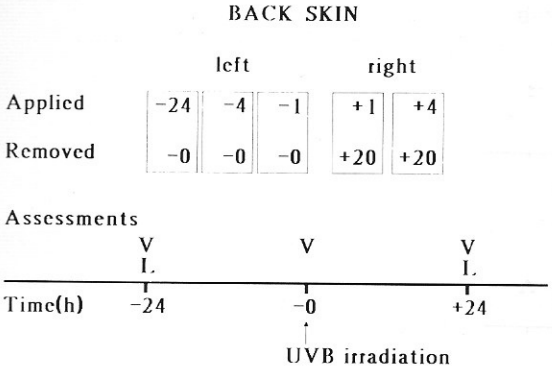

Fig. 1. Course of the study. Acrylic tape strips with 10–11 large Finn Chambers® filled with 50 µl of test substances (see Table I) were fixed 24, 4 and 1 hours before, and 1 and 4 hours after ultraviolet light B (UVB) irradiation. V=visual assessment, L=laser Doppler flowmetry.

test substances and fixed 10 mm apart from each other. Sets of 11–12 Finn Chambers® were fixed on the back 24 hours, 4 and 1 hours before UVB irradiation (Fig. 1). The test tapes were removed just before irradiation and the test substances were carefully removed with soft paper towels in order to minimize their optical effects on the skin. The test sites were then inspected in order to exclude any patients with allergic or irritant reactions. Only test sites were irradiated and the surrounding skin was protected with strips made of black plastic adhesive (d–c fix®, Konrad Hornschuch AG, Weissbach, FRG) with holes 8 mm in diameter. The creams were also applied 1 and 4 hours after irradiation and removed after 19 and 16 hours, respectively (Fig. 1).

Grading of the test reactions

The visual grading of the test reactions was performed 24 hours after irradiation, and was from − to +++ (−=no reaction, +=faint erythema, ++=moderate erythema, +++=intensive erythema and oedema).

All test sites were also measured with a laser Doppler flowmetry device (Periflux®, Perimed KB, Stockholm, Sweden) (22) before the application of any test material and 24 hours after the irradiation.

Table I. *The test substances and their concentrations*

Substances other than commercial preparations were incorporated in an o/w cream which was also used as the cream control

Substance	Concentration, w/w (%)
Hydrocortisone	1
Hydrocortisone-17-butyrate[a]	0.1
Betamethasone-17-valerate[b]	0.1
Betamethasone-17,21-dipropionate[c]	0.05
Indomethacin	1.0
Indomethacin	5.0
Acetylsalicylic acid	5.0
Butylhydroxytoluene	0.1
Butylhydroxytoluene	1.0
Diphenhydramine hydrochloride[d]	0.2
Controls	
o/w cream	
Empty Finn Chamber®	

[a] Locoid® cream, Gist Brocades N/V, Delft, The Netherlands.
[b] Bemetson® cream, Orion Pharmaceuticals, Espoo, Finland.
[c] Diproderm® cream, Essex Lääkkeet Oy, Espoo, Finland.
[d] Medidryl® cream, Huhtamäki Corp./Medica, Helsinki, Finland.

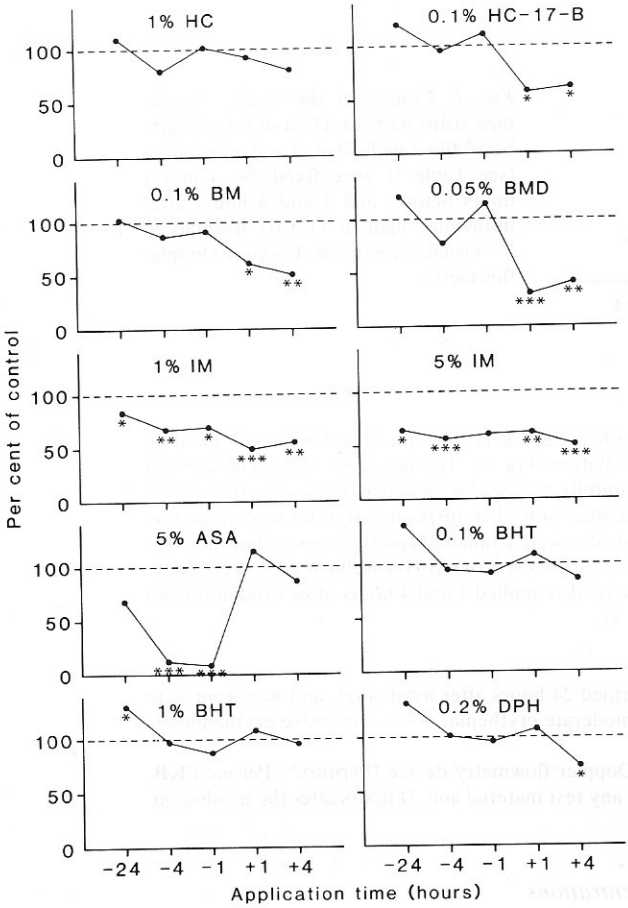

Fig. 2. The intensity of UVB erythema on test sites (per cent of that on cream control site). The test preparations were applied both before (−24, −4 and −1 hours) and after (+1 and +4 hours) UVB irradiation, removed after 24, 4, 1, 19 and 16 hours, respectively, and measured with a laser Doppler flowmetry device 24 h after irradiation. HC=hydrocortisone, HC-17-B=hydrocortisone-17-butyrate, BM=betamethasone-17-valerate, BMD=betamethasone-17,21-dipropionate, IM=indomethacin, ASA=acetylsalicylic acid, BHT=butylhydroxytoluene, DPH=diphenhydramine hydrochloride. $*p<0.05$, $**p<0.01$, $***p<0.001$ (paired *t*-test).

The measurements were made in an operating theatre, at a temperature varying between 22.5°C and 25.5°C. The selected output-circuit constant of the laser Doppler device was 0.2 sec, the bandwidth upper limit 4 kHz and the gain 10. Before each measurement the test subject rested on a chair for five to ten minutes. The axillar temperature of the test subjects varied between 36.0°C and 37.1°C (mean 36.6°C), the pulse rate between 56 and 104 (mean 76). The change in the blood flow of the skin was then calculated.

Paired *t*-test was used for statistical analyses.

RESULTS

When applied before irradiation, 5% ASA and 5% and 1% IM significantly reduced the reaction to UVB (Fig. 2). When applied after irradiation, IM, DPH and topical steroids (except hydrocortisone) showed some inhibitory effect on UVB erythema, but 5% ASA had no effect (Fig. 2).

Overall unanimity between the visual and laser Doppler assessments was good, for which reason only the laser Doppler values are presented (Fig. 3).

DISCUSSION

In the present study the chamber technique proved to be efficient in testing how a great number of substances affected UVB-induced erythema, thereby allowing interindividual comparison of the test results.

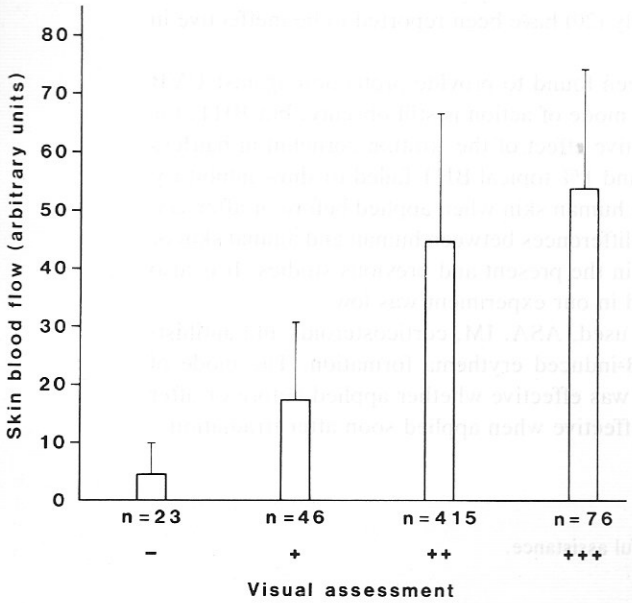

Fig. 3. The relationship between the visual assessment (−, +, ++, +++) and the corresponding means of laser Doppler measurements at 24 hours after UVB irradiation.

The non-steroidal, anti-inflammatory analgesics inhibited UVB-erythema significantly when applied before UVB irradiation, acetylsalicylic acid being more effective than IM. Earlier studies have shown that IM inhibits UVB erythema in rat and human skin when administered orally before irradiation (10, 15), when injected intradermally after irradiation (6) and when applied topically before or after irradiation of guinea pig and human skin (7, 17, 18). Topical IM also inhibited UVA-erythema in human skin when applied before or after irradiation (18, 19). Peroral ASA taken before or after irradiation has been found to reduce UVB erythema in human skin (5, 15). Topical acetylsalicylic acid is effective in reducing UV erythema in rats when applied immediately after irradiation (10). In the present study, when applied after UVB irradiation, 5% ASA cream showed no inhibition of erythema, in contrast to both 1% and 5% IM. This finding may be because IM is a more potent anti-inflammatory agent than ASA, and its mode of action may differ from that of ASA.

In topical preparations, salicylic acid, at 0.1% or more, has been found to have a topical photoprotective effect of up to 60% that of para-aminobenzoic acid (8). IM absorbs both UVB and UVA radiation (18, 19). We also measured the absorbance of ASA and IM in absolute ethanol, and found that 5% ASA absorbed as much UV in the range of 280–320 nm as did 1% IM, but as to the absorption of longer wavelengths, ASA was significantly inferior to IM. Our UVB source, Sylvania F 75/85W UV6 tube, is not a pure UVB irradiator. However, the amount of UVA is so low that it obviously had no effect on the results.

Topical corticosteroids inhibit UVB erythema in human skin more readily when administered after irradiation (4, 9, 12, 14). Our results confirmed previous findings, and showed the effect of corticosteroids to be maximal when applied one hour after irradiation. The order of efficacy was the same as that of potency: betamethasone dipropionate > betamethasone valerate > hydrocortisone butyrate; hydrocortisone was ineffective.

DPH at 0.2% showed a nearly significant ($p<0.05$) inhibition when applied four hours after irradiation, suggesting that histamine may play some role in the early phase of UVB-induced erythema formation. Diphenhydramine, promethazine and cimetidine injected

intradermally (16) and terfenadine given orally (20) have been reported to be ineffective in the inhibition of UV-induced erythema (16).

Systemic and topical antioxidants have been found to provide protection against UVB erythema in mice and rabbits (11, 13). Their mode of action is still obscure, but BHT, for instance, seems to enhance the photoprotective effect of the stratum corneum in hairless mice (21). In the present study, both 0.1% and 1% topical BHT failed to show inhibitory or protective effects against UV erythema in human skin when applied before or after UV irradiation. This discrepancy may be due to differences between human and animal skin or to the difference between the vehicles used in the present and previous studies. It is also possible that the concentration of BHT used in our experiment was low.

In conclusion, of the topical preparations used, ASA, IM, corticosteroids and antihistamine showed an inhibitory effect on UVB-induced erythema formation. The mode of action of ASA may be photoprotection. IM was effective whether applied before or after irradiation. The corticosteroids were most effective when applied soon after irradiation.

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