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Effect of Drugs on the Early and Late Phase UV Erythema

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The inhibition of erythema by drugs applied topically after irradiation with 0.2–0.8 J of 313 nm has been studied in healthy volunteers. Indomethacin and piroxicam markedly inhibited the erythema at 6 to 24 h after irradiation but erythema reappeared at 45 h. The results reported suggest that the UVB response is biphasic with an early phase responsive to nonsteroid anti-inflammatory drugs and a late phase which is not responsive. No effect on the intensity of the erythema was seen with betamethasone chloroquine and cetirizine. Oral intake of aspirin before and/or after irradiation did not influence the UV response.

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Systemic and topical administration of potent corticosteroids and nonsteroid anti-inflammatory drugs such as aspirin, indomethacin and meclofenamate can inhibit UVB induced erythema when applied after irradiation (1–9). Antioxidants can protect against UV erythema in animals but have no effect on human skin (9). Antihistamines have usually been found to be ineffective (10–11).

In most studies the UV erythema was estimated 20–24 h after irradiation. The present study was undertaken to investigate the effect of drugs on the erythema when measured at prolonged times after irradiation (6–72 h). Farr & Diffey (6) have previously described the time course of the UVB and UVC erythema reactions in human skin. They noted that topical indomethacin only partly reduced the erythematous response up to 36 h after irradiation with 300 nm. Our aim was to better understand why drugs selected for their anti-inflammatory properties in the human UV erythema model give disappointing results in the treatment of skin diseases with a strong inflammatory component such as psoriasis.

MATERIALS AND METHODS

Twenty healthy volunteers (10 men and 10 women, age range 24–50 years, skin type II-III) participated in the study. They were neither tanned nor were they taking any drugs, except contraceptive pills in 5 women.

Photo irradiation apparatus and procedure

We used a monochromatic irradiator (Clinical Photoirradiator, Applied Photophysics Ltd, London, UK) set at 313 nm and equipped with a round outlet head of 20 mm^2 (diameter of 5 mm) which was pressed slightly against the skin. The irradiation emitted was measured at each test procedure by a built in dosimeter. The following doses were administered on the back: 0.2, 0.4 and 0.8 Joule. Pretests had shown that the minimal erythema dose was 0.2 J for most subjects. The time needed for the lowest dose was 15 sec. Immediately after the irradiation the drugs were applied to, and just around, the tested area by painting with a cotton swab. The drugs were dissolved in ethanol if not otherwise stated (Table I). The controls were treated with only the solvent. The treated area was then covered with a hydrocolloid dressing (Actiderm®, Convatec, Squibb, USA) which was left in place until examined. When a clear erythema appeared it could be detected through the transparent dressing. For accurate grading the dressing was removed. The minimal erythemal dose was for most subjects 0.2–6 h. After the reading at 6 and 18–24 h the drug was reapplied as before and a new dressing was applied. In all subjects a reading was performed at 45 h after irradiation and at the 72-h time point a final reading was carried out in 10 subjects. In 4 subjects 500 mg aspirin was given orally immediately after irradiation and every 6 h for 3 days. New test sites were irradiated at 6, 24 and 48 h after the first intake of aspirin.

Grading of the test reactions

A visual grading of the UV-induced erythema was used: 0 = no reaction, 1 = hardly visible erythema, 2 = faint but clear erythema, 3 = moderate erythema, 4 = marked erythema with some edema and 5 = very intensive erythema with edema. Grading was performed by the same person under similar ambient conditions of light and temperature. The observer was unaware of the nature of drugs applied.

Drugs tested

The drugs tested and the concentrations used are given in Table I. Tests with cetirizine and chloroquine were performed on 6 subjects. Tests with indomethacin piroxicam and betamethasone were carried out in 20 subjects with a certain modification in the number of applications. In 6 subjects the drugs were reapplied at 6 h, in 12 at 18 h and in 6 also at 24 h.

RESULTS

The response of normal skin to UV irradiation showed a time-related profile with a maximal erythema response developing at 12–24 h and which remained for at least 45 h. At 72 h the mean erythema of 10 subjects had slightly decreased and some pigmentation was also seen. Under similar irradiation conditions in the presence of indomethacin, applied topically under occlusion, the erythema was not observed before 6 h post-irradiation after which time a steady increase in the response was noted, which at 45 h was similar to that observed in the absence of indomethacin. Fig. 1 shows the results with 0.4 J. Similar curves were seen with 0.2 and 0.8 J. No difference in

Table I. *The drugs tested and concentrations used*

Drug tested	Concentration and solvents used %
Betamethasone dipropionate	0.05 e
Betamethasone valerate	0.1 e
Cetirizine	1 e
Chloroquine	1 w
Indomethacin	0.3e
Piroxicam	1 chl+e

Solvents used: e = ethanol, w = water, chl = chloroform.

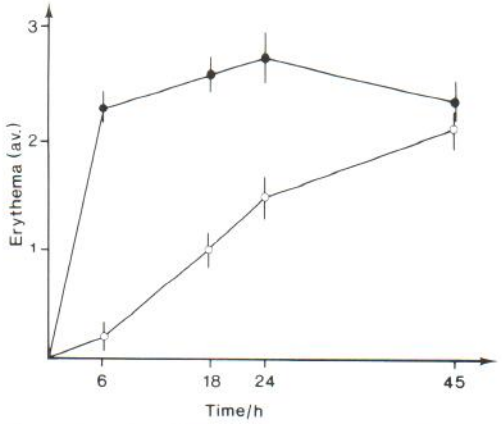

Fig. 1. Average grade of erythema observed in 20 subjects after irradiation with 0.4 J. [Control area ●—●. Indomethacin-treated ○—○]. Vertical bars indicate SEM. The difference between indomethacin-treated and control skin was significant at 6 and 18 h ($p < 0.001$) and at 24 h ($p < 0.02$).

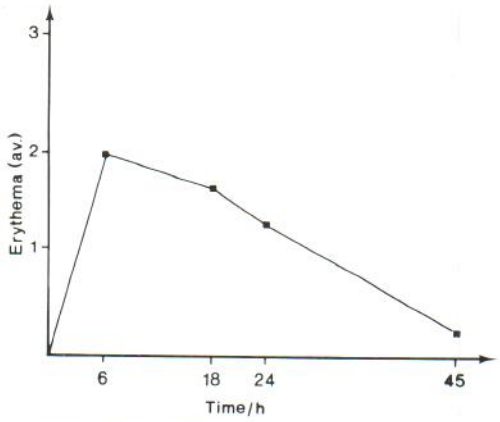

Fig. 2. Estimated time course of the acute phase erythema reaction obtained by subtraction of the indomethacin and control curves shown in Fig. 1.

effect of indomethacin was found in 3 subjects when 0.1, 0.3 and 1% were applied. All further experiments with indomethacin were carried out at 0.3%. Piroxicam when applied topically also produced a significant delay in the onset of the UV-induced response.

Corticosteroids produced blanching at the application site, but the irradiated zones presented an erythematous response. The degree of reddening at the 6–18-h time point post-irradiation was the same as observed in the non drug treated control area in 14 subjects and only slightly weaker in 3 subjects.

Chloroquine and cetirizine applied topically as described above did not influence the UV response. In addition the UV erythema was uninfluenced by repeated oral intake of aspirin either before or after irradiation.

DISCUSSION

Previous investigators lead us to believe that cyclo-oxygenase inhibitors such as indomethacin effectively inhibit UV-induced skin erythema (6). This action is also readily observed in the guinea pig. Our study focuses attention to the time course of the reaction. Modulation by prostaglandins may explain the acute response (6–24 h) to indomethacin and piroxicam but other mechanisms should be invoked in order to explain the erythema observed after 48–72 h. Some similarity can be seen with observations made in the pharmacology of inflammation provoked by dithranol, which could not be suppressed by a wide range of topically applied drugs. The present work is now being pursued at the immuno-histological levels with a view to identify the presence of late phase cytokines secreted by keratinocytes in response to the UV challenge.

The results reported here point to the possibility that the human response to UVB is biphasic. The early phase is not responsive to an antihistamine or chloroquine whereas the non-steroid anti-inflammatory drugs such as indomethacin and piroxicam inhibit the early phase. None of the drugs tested affected the late phase. A closer look at the time course of the indomethacin action leads us to propose that anacute erythemal onset is initiated between 6–12 h after irradiation and minimizes at 45 h (see Fig. 2).

The behavior of corticosteroids warrants special attention. Corticosteroids have been reported to inhibit the erythema induced by 1–2 minimal erythema doses but not with higher doses (7). These results have also been confirmed by us when irradiating 1–2 dm^2 areas (300–360 nm) and treating them just after irradiation with betamethasone. It is evident that the vasoconstriction will interfere with the interpretation of the data.

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